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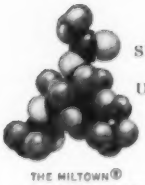

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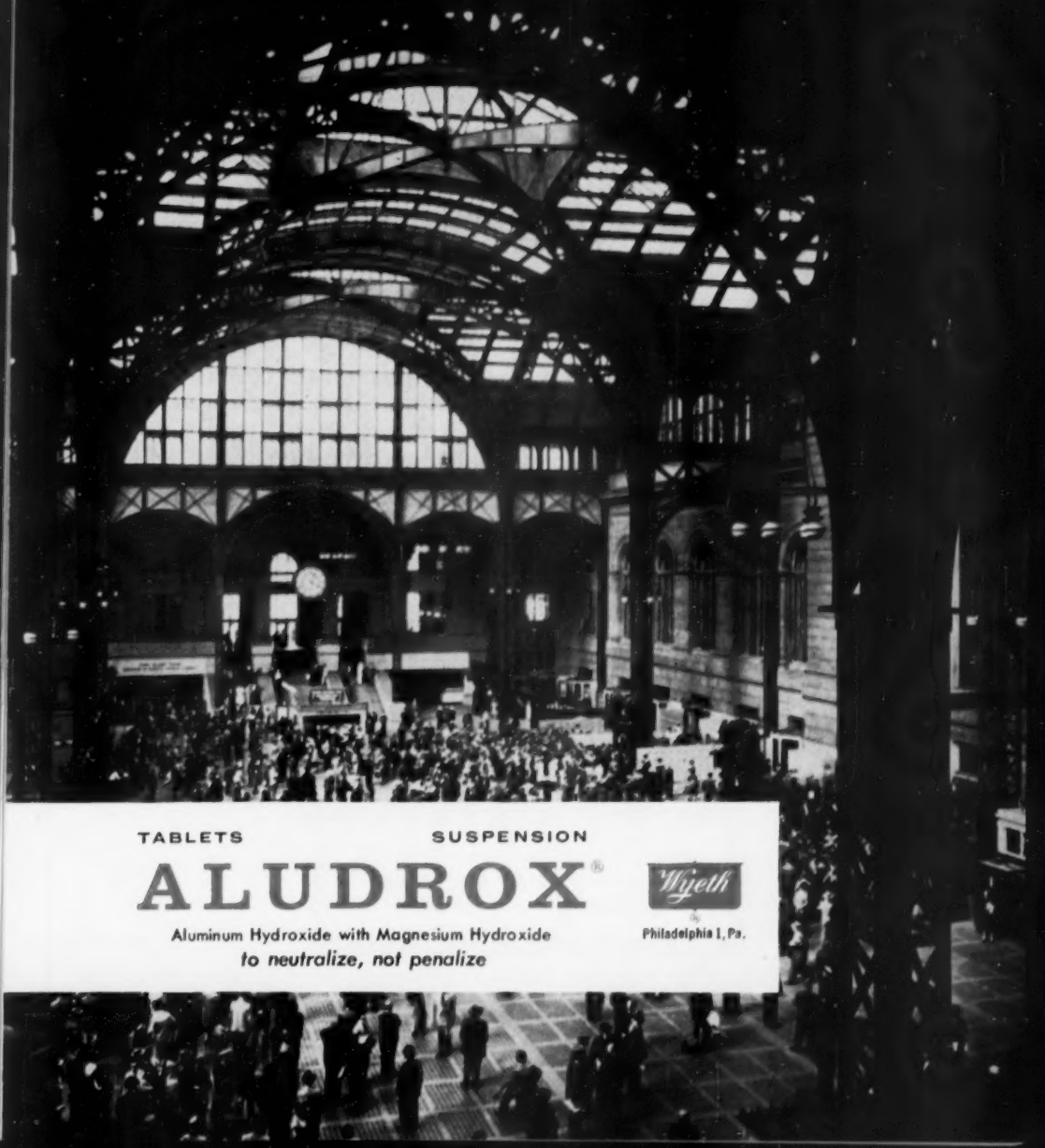

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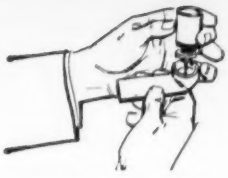

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1. Conner, P. K., Jr., and Moyer, J. H.: *GP 14*:124 (Nov.) 1956.
2. Kinney, J. J.: J. M. Soc. New Jersey *53*:128 (March) 1956.
3. Weil, L. L.: Florida J. Gen. Pract. *4*:9 (July) 1954.
4. Report of Study by Army, Navy, Air Force Motion Sickness Team: J.A.M.A. *160*:755 (March 3) 1956.

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Cereal Institute, Inc.: The Nutritional Contribution of Breakfast Cereals. Chicago: Cereal Institute, Inc., 1956.
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Editorial

Careers in Medicine

Some Inquiry into "Why We Study Medicine" and "Why We Specialize"

WILLIAM BENNETT BEAN, M.D., Iowa City

Types of Doctors

The medical profession, in respect of the spirit in which they pursue their occupation, may be divided into four classes, corresponding to four classes of clerical teachers: 1st, Those who have been put into the profession, or chosen it at random, because they must be doing something—loungers who feel their business a toil and a constraint, who at best only desire to escape disgrace and make a living—correlative to the gentlemen in orders, and the drudging curates—a very unprofitable race when gentleman, a very unhappy and mischievous one when otherwise. 2nd, Those who pursue their trade eagerly and diligently for money or advancement—correspondent to the preferment hunters of the Church, and the popular preachers and Tartuffes of all denominations, who will generally be respectable or otherwise, as their rank or connections give them more or less of character to lose. 3rd, The votaries of science, to whom knowledge is an ultimate object, and practice chiefly valued as the means of increasing and certifying knowledge—correspondent to the speculative theologians—the students of religious learning—a class highly estimable and necessary, who answer their vocation well, and dignify their rank, whatever it may be: and 4th, The philanthropists, to whom knowledge is only a secondary object, valued as the means of abating pain and preserving life—correlative to those Christian teachers and pastors who are animated with the true and faithful love of souls. Among these, it is delightful to find men of all ranks—but rank with them is nothing: these are illuminated with a light, in which there may be many colours, but there is no darkness . . . . Hartley Coleridge, Life of Dr. John Fothergill.

Three Views of the Physician

I remember that as a growing boy a special reward for some rare and now forgotten deed of virtue was to be allowed to look at my father's folios of anthropological lore. A favorite book contained figures from the wall of the cave of the Three Brothers in the Pyrenean hills of the province of Ariége, deep in the south of France. Not only were the animal pictures delightful but the Cro-Magnon artist of some twenty thousand years ago had represented early man with fine perception. One very striking picture was that of a man clothed in a deer skin and wearing as head dress the deer's antlers. In his crouching position, his head was cocked to peer straight at those before him with penetrating almost hypnotic stare. The same awe which his fellow tribesman felt was certainly part of my reaction. Only later did I realize that here, in fact, was the first portrait of a physician. His representation in the guise of a primitive witch-doctor emphasizes the grotesque paraphernalia needed to fix the attention of the sufferer and divert him from his pain. Also the atmosphere of fear and horror helped to make strong the faith in his power to heal.

Early peoples attributed disease to supernal and external forces. It was the doctor's job to find what spirit was causing the trouble and then overpower or out-wit him by appropriate ceremony and remedy. Intuitively the magico-religious healer, the priest physician, perceived some of the relations of emotions, social pressures, supports and customs upon health and sickness. Rarely an herb, weed or other medicine might have some actual pharmacological property, but this could not be understood. The major therapeutic virtue was the psy-

Submitted for publication Feb. 18, 1957.

This address was presented at Little Rock, Ark., May 23, 1955, at the installation of a chapter of Alpha Omega Alpha, and to many other groups of medical students. It will appear also in the spring issue of *Pharos*.

chological value of ritual and magic. This won the patient's confidence by showing him that the cause of the trouble had been overpowered and removed. Failure was attributed to the overwhelming strength of the supernatural. Success was always credited to the doctor who therefore exerted tremendous *power* and authority in a community—to be used for beneficient ends by the good, sinister ends by the unscrupulous. For whatever end the mainspring in motivating the earliest physician was the desire for strength or power, to dominate, to be king, though there must have been an admixture of tenderness and humane care. Desire for strength and power made tolerable the long and painful apprenticeship to the exalted position of priest-physician.

Much later Imhotep, whom Osler called the "first figure of a physician to stand out clearly from the mists of antiquity," my second physician, exerted much the same influence through the same employment of amulet and ritual, incantation and incense. But by this time empirical wisdom, the trial and error of a thousand crude tests, was getting fixed in the written record. Physicians were now employing emetics, purgatives, diuretics, enemas, sweating agents and even bleeding. Sometimes harmed, sometimes helped, often comforted, rarely cured, man survived more from innate toughness than because of specific therapy, justly applied. But the physicians of the time of Imhotep were reacting to the urges of curiosity and *wonder*. While they did not dream of the experiment in our sense they wondered and puzzled, observed and recorded. They took advantage of nature's experiments. Thus, wonder or curiosity as a major stimulus is the second historical reason why we become doctors.

A third physician is exemplified by the rude practitioner, called in by the peasants of Perche, in France. As Fraser tells us in the "Golden Bough," it is common knowledge in those parts that a prolonged fit of vomiting is caused by the stomach's becoming unhooked, as they call it, and so falling down. Naturally the physician's role is to hook the stomach up again. Accordingly, after a brief inquiry tells him what is wrong, the physician at once throws himself into the most horrible contortions, crying and writhing in order to unhook his own stomach. Once he gets it unhooked, he undergoes another and opposite series of twists, turns and grimaces. This of course hooks it up again. With the migrant tripes once more nestled snugly against the midriff, the patient experiences corresponding relief. This extravagant behavior is the archetype of the bedside manner. It has behind it, not the fee (a mere few francs) but the altruistic motive of the physician to bring help to the sufferer. *Altruism* is the third major force leading us to become doctors.

Cotton Mather records such a phenomena in the too solicitous "Husbands who breed for their Wives; and the while they for diverse Months have the Satisfactions that they suffer not one Moments Disoreder. Yea, we have known several Husbands carry the Good Humour so far, as to Travail for their Wives . . . and have the Gossips attending on them while their Wives have brought forth the Offspring with scarce a Groan upon it."

While this look backward oversimplifies the problem it is my purpose to examine to what degree altruism, a sense of wonder, and the drive for power have influenced men in the selection of the profession of medicine as a career. These three forces are major impulses leading us into medicine. If you allow me some latitude I think we may include the significant ones under these three.

My comments will occupy the terra incognita between the mystical probings of the psycho-analytically inclined psychiatrists dredging into the past for motives they claim drive and hurry us along, and the sometimes discouragingly dry data of the less imaginative scientist who collects sex habits and wasp wings with detached indifference. It depresses me that to him one

is as interesting as the other. If my remarks have little of the penumbra of the statistical mists of Kinsey I hope they will also escape the sex-cathedra pontifications of the Freudians. Nor will I stress the guilty and well kept secret of modern psychiatry and psychology that we know more about why and how rats get food in mazes than why people go into a profession or calling such as medicine. But this is no time to belabor psychiatry. In it lies some hope for the future; for its wisest practitioners know well and are deeply frustrated by their inability to apply strictly the scientific rules of biology to its peculiar problems.

Each generation of aspiring undergraduate medical students is motivated by their mental images of the previous generation of physicians; each group of doctors aims to treat their mental images of diseases they studied in school, regardless of how the patterns of disease may shift. Motives for studying medicine may play one false if there are sudden or sharp changes in medical mores. As an example of a shift in the public's ideas about physicians, Dr. Watson in "Sherlock Holmes" was respected. He was rich in deportment if not in wisdom. In today's detective story any physician is a prime suspect as villain or accomplice in I know not what nefarious crimes. This is accepted without question or murmur.

I am getting old enough to look with alarm at the younger generation but I suspect most of the traditional fretfulness of elders with youth is born not of wisdom but of forgetfulness. I do not subscribe to the notion that today's youth is prematurely old, a generation brainwashed by fear to the extent that it no longer rebels. Certainly it is not the exclusive prerogative of youth to react to the H bomb with feelings of futility. Perhaps, though, it is reason enough why hard work is avoided, with great skill (and effort), why present mediocrity with a modicum of security is accepted against the uncertain future of higher accomplishment. As motives degenerate achievement becomes less impelling than security. Still, those with the most original and independent minds will regard security as a poor substitute for freedom. To people in this class which you belong to, I am addressing my remarks.

What are the reasons, we shall want to know, why anyone wishes to enter a career to which the approaches are difficult, the apprenticeship full of trouble, the work long and hard, the goals so distant? And at a time when science's capacity for actual accomplishment is at the upper end of the see-saw while respect for medicine is at the bottom? In an idle moment I listed some seventy-five substitutes for the physician which today's folk lore may urge upon those who are sick or who think they are. This includes quacks and cultists of every kind, patent medicines and machines and the purveyors thereof; the spa, bath or gymnasium; books, journals, newspapers; exercisers; food fads; sunshine; travel; moves to new places; vibrators and massagers; adjustors and maladjustors promising cures of all sorts; and the do-it-yourself skullduggers recommending self-diagnosis and self-treatment but rarely disclosing the sequel, self-sacrifice.

The Motives

No problem in the whole realm of psychology resists exact formulation more rigorously than that of man's motives. We may forecast, contemplate and review but at best this gives us a sparse yield of firm facts. In short we can never know all the changing patterns of forces which shape and design our careers. All will agree that chance and luck, free will and plan, and hard necessity are determinants of varying intensity in any decision.

Of those who enter the profession of medicine by chance there is little to say. My surmise is that for every one thus deflected into medicine many are turned away. No one will deny that chance played a part in leading each of us into medicine. But chance is a factor outside the range of the analysis of motivation.

The role of emulation is hard to evaluate, but as a general force it is important whether we wish to model our career on the charity, curiosity, or cupidity of our hero. What the psychiatrist calls identification, the wish to become and be like our hero, is a subtle but strong influence. A doctor who has come to help us in our time of need plants the seeds of a strong desire to emulate him. Or we may be moved by wonder at how he knew what was wrong and what to do. Curiosity may be directed at the true inwardness of medicine or at the process by which practitioners acquire their knowledge. And emulation tinged with envy at the mansion or Cadillac may supply the model we aim to copy.

Emulation in a more traditional approach to medicine may operate as a family trait. Sons and grandsons of physicians follow in their path, having a sense that that was their foreordained lot. So strong may be this feeling that persons with no mental or temperamental fitness for medicine follow the line of least reaction to explicit or implicit family pressure. Those who drift into medical school from such a background are lucky to extricate themselves before the evil tangles of frustration overwhelm them. But a parent's desire may have all the force of final law and may carry the day. Then we merely have to examine the reasons why a father wants his son to follow in his footsteps. I submit that the motives are not different from those intrinsic in the putative physician who pursues his course independently. Perhaps superficial reasons of status are stronger here. Whatever the reason, it is true that professional families provide a large element of replacements, even with a good deal of interchange from one profession to another. Fielding Garrison, Freud and Helmholtz are examples of men who went into medicine at their father's insistence or suggestion.

Some physicians enter medicine as an escape from parental pressure toward some other career. In this case the parental influence backfires. The relative lack of importance of family tradition and parental pressure in our culture may be seen in the scarcity of families with physicians for more than three consecutive generations.

Another motive for becoming a doctor is the lack of motive. Then medicine is a last resort. Marion Sims analysed his reasons for entering medicine as follows: "A graduate of a college had either to become a lawyer, go into the church, or to be a doctor. I would not be a lawyer, I could not be a minister, and there was nothing left for me to do but to be a doctor—to study medicine or to disgrace my family." Welch, wanting to break with his family medical tradition and be a Greek scholar, failed to get a coveted appointment. Thwarted in ambition and beaten down by circumstance he entered medicine by the back door. But medicine for him was not the life of a family doctor but as a manipulator of ideas and an innovator in teaching. Franklin Martin wished to escape the farm boy's lot behind the plough for that of the physician of elegance drawn in a carriage. Oliver Wendell Holmes used a medical career to escape the law, while his son reversed the process. Charles Caldwell, that waspish old medical gossip, became a doctor because his family would not let him study law or become a soldier. Victor Heiser had been a jack of many trades before turning to medicine. Thus we have records of many notable physicians who were in a corner and turned to medicine as a way out.

Women in medicine require separate treatment. Of all the many generalizations I make these are most beset with error. A woman should be spokesman here. The early woman in medicine had little of the altruistic motivation which led Florence Nightingale to resuscitate nursing and establish it as an honorable profession. The drive goading the first women physicians into a medical career must have been largely an expression of the feminist movement. They must be equal to men even if they were not. In essence the motive was the same that caused the suffragette to lash out at men in general. It made life pretty exciting for men. Today when it has been found that with each right comes a duty the militant suffragette, rest

her colorful soul, is no longer with us. This motive is gone. Even so medicine is one of the few careers in which a woman can attain intellectual parity with men, and at the same time some social and financial independence. I must not be chided if I say that in my experience most women go into medical school to find a husband. Of all the motives which lead people to be physicians perhaps this is the most natural.

There is a whole miscellany of alleged motives which defy exact classification. Roger Lee "always had the idea that he was going to be a doctor." Many seem to recall no time when they were going to do anything else. Somerset Maugham went into medicine for reasons of snobbery. James Fisher's girl would not marry him as a veterinary surgeon so he became a physician. William Carlos Williams and A. J. Cronin wanted support for a literary career. Stanley Cobb was complemented by a surgeon for manual dexterity. Reading a medical biography influenced Havelock Ellis. John Bunyan, in a pleasant passage from "The Jerusalem Sinner Saved; or, Good News for The Vilest of Men" tells us of desire for applause and fame as motives:

> Christ Jesus, as you may perceive, has put himself under the term of a physician, a doctor for curing of diseases; and you know that applause and fame are things that physicians much desire. That is it that helps them to patients, and that also that will help their patients to commit themselves to their skill for cure with the more confidence and repose of spirit. And the best way for a doctor or physician to get themselves a name is, in the first place, to take in hand and cure some such as all others have given up for lost and dead. Physicians get neither name nor fame by pricking of wheals, or picking out thistles, or by laying of plaisters to the scratch of a pin: every old woman can do this. But if they would have a name and fame—if they will have it quickly, they must, as I said, do some great and desperate cures. Let them fetch one to life that was dead; let them recover one to his wits that was mad; let them make one that was born blind to see; or let them give rip wits to a fool; these are *notable cures;* and he that can do thus; and if he doth thus first, he shall have the name and fame he desires; he may lie abed till noon.

But now let us come to the main motives—love, wonder and power.

Recognizing that multiple causes always operate, and that motivation is not the nice detached datum we should like, I will select a few examples. Physicians egotistical enough to write autobiographies and sensitive enough to introspect their own motives gives us a sample with hopeless bias. This is rectified only a little when biographers interpret their motives for us.

I begin with charity, the old Latin *caritas*. My first example is Jean Fernel, scholar, innovator, teacher and busy family physician who made two great advances. First, he freed Renaissance medicine from the chains of astrology which built a false prognosis based on horoscopes. Next he eliminated the mystic operations of magic which shackled medicine with superstition and kept observation and experiment from taking their rightful place in medical thought. What do we know of this strange man—Jean Fernel—who comes stalking into clear light out of the confused and mystic medical notions of his time. To help orient myself rather than you—when Fernel was twelve, Henry VIII became King of England. When he was 25, Magellan's crew completed their voyage around the world. When he was 38, Rabelais' "Gargantua" was published and to keep the balance even for that year, the Jesuit Order was founded. When he was 46, Copernicus published his epochal work on "The Revolution of the Celestial Spheres." When he was 56, Servetus was burned as a heretic in Geneva.

Fernel was trained at the University of Paris where he was exposed to the full flowering of humane letters. Beautifully made and relatively cheap books were swarming from the fertile printing presses. Even after he had his M.A. degree at 22, Fernel decided to go back to a detailed study of Latin and Greek so that he could completely master the classics. Besides reading and studying logic, mathematics, grammar and rhetoric, which he did unremittingly for five years, he seems to have had no partic-

ular career in mind. Then when he was 27, he was laid low by a quartan fever, left Paris for the countryside, fresh air and a slow convalescence. There the question of a career forced itself upon him. Before him lay the choice of the church, law or medicine. He chose medicine. To Fernel's natural disposition to scholarly inquiry, his severe illness demonstrated the essential beneficence of medicine. For his further training he supported himself by giving public lectures on philosophy and by serving as a tutor for children of several important families. He later became almost equally famous as a practitioner, a teacher and a medical thinker. That he brought marvelous energy to his career is indicated by his 19 hours of activity beginning at four A.M. with study, breakfast at daylight, patients in the morning, teaching in the afternoon, writing in the evening, bed at eleven P.M.—a veritable prodigy of activity even for that very active period. His medical philosophy he summed up in the following words:

> Is there a greater blessing vouchsafed to mankind than medicine is? Life is our dearest possession by which we breathe and enjoy the company of our fellow beings.
>
> Can any calling be worthier than that which preserves and maintains life itself?
>
> Is wealth or fortune in whatever measure in the last analysis more estimable than is good health?
>
> Is any misfortune or disaster more grievous than ill health?
>
> He who succors the sufferer and the sick excerciseth a knowledge which deserves the admiration and affectionate regard of all men.

My other example is Albert Schweitzer, a contemporary whose story perhaps has been overtold. But it bears retelling. As a boy and young man an intense feeling of love for his fellow man was a moving force rather than a misty dream. Having reached a peak of excellence as an organist, with a choice of a great career in this field he decided to become a physician to minister to the miserable people in a most forlorn part of Africa. His story, told with beauty and eloquence, barely does justice to the heart warming nobility of the man, his character and his deeds. This stands as a monument to mans natural dignity and a reminder to the cynic that love and altruism are not dead.

It is somewhat harder to document curiosity as a force which brings young people to a career in medicine. When the force is very strong it may stop short in the preclinical sciences which claim some who originally aspired to practice medicine. Hans Zinsser, in his charming autobiography, written by himself as the strip-tease artist for a flimsily veiled alter ego, describes at some length his approach to the science of bacteriology through an apprenticeship in medicine. To begin with he wanted to be a writer. He was advised not to try a career in belles-lettres. His teachers then stimulated a natural curiosity and turned him in the direction of medicine. This he used consciously as the only accepted approach to bacteriology. His medical training was a fine background for his epidemiological and clinical studies. His interest in and cultivation of the fine arts makes him one of the exceptional physicians whose urges to write, the *cacoëthes scribendi,* found the author equal to the task—one of the rare physicians who may be read by the perceptive without painful trauma.

I have for a long time been interested in Sir William Osler, who as a physician seems clear enough, but who as a person strikes me as an enigma. His biographers and disciples have left many questions not only unanswered but unasked. A curious paradox is that the path leading him from the ministry to medicine had as trail blazers staunch clergymen with an avid interest in natural history. The steps from diatoms to parasites to higher animals to man were followed in a logical sequence along the microscopic pathway. A rich and sustained wonder in the world about was the apparent motive. Osler did not leave us much in the way of personal introspection to examine. His capacity for absolute concentration and his personal amputation of the past and lack of concern for the future might set the psychiatrist dreaming but I find little to fix on

as fact. At least one of the strong motives leading him to medicine was curiosity. His ability to keep his own alive and stimulate it in others is one of the measures of his greatness. We are thankful that it found another focus in digging into the past history of medicine which he illuminated in many elegant essays.

Autobiographical admissions that the desire for power in any form led to medicine are not to be found. Biographers have hinted at it. I shall not trot out any black list of those who admitted going into medicine to obtain money and power. We can all name those we know. They gravitate into areas where they believe they will obtain the largest financial returns. Some are in all fields. Most are specialists, and generally those who exploit some technique. The brevity of this section is no indication that this is not a very, very important force. I simply prefer to to call names.

Specialization

Having considered why we are led to a career in medicine we may look at the possible motives which direct us into a particular specialty. Whatever the reasons for studying medicine, the first year student enters medical school with only the haziest notions of medical practice, economics and politics. Even if respect and admiration for his family physician got him this far, new and disturbing elements are fermenting. His own family no doubt has called to his attention the dilapidated old car of the practitioner and the fancy model of the surgeon or dermatologist. Pressures during medical school are strong. Too often they force a student away from the most suitable career into one with elegant externals. Present day teaching is done by specialists in large hospitals with at least some element of ivory tower. The patients are those whose problems are beyond the scope of the general physician, or are examples of errors in diagnosis or treatment. Representing but a small fraction of his practice, the errors are exposed in glaring light and the practitioner is held in low esteem. But the main fault has been the lack of interest in general practice. The decline of the family doctor may reflect a decline of the family. Till recently general practice has had little attention and less constructive thought from medical educators, specialists or indeed the public at large. Part of the bad press of medicine results from the failure of the general physician to be an effective spokesman for his cause or to find one. Much criticism is against situations no longer prevalent. It is the traditional prerogative of the public to criticize but the confusion of both the public and the doctor has resulted in lack of understanding and appreciation which has put medicine in a bad light.

The man with sound training in the principles and practice of medicine, doing general work, offers intimate personal service to patients who can turn to him at all times and all places when in need. Sound diagnosis and therapy assure him a satisfying existence and a satisfactory practice. No other physician has what he has to offer or can expect such personal satisfaction. The experienced physician in rural and semi-rural areas has a place in community life no other doctor has and indeed few others in any profession have.

The history of specialization in medicine goes back as far as we have any records at all. It is hinted at in the fragments of Egyptian records in the papyrus. The medico-religious cults of Rome paid tribute to God and Caesar simultaneously in a system of minor tutelary dieties with a specialist god for each separate trouble. Even the itch had Scabies to call upon. And there was Angina for quinsy and Febris for malaria. Fixtula and Hernia had their niche in the feminine theocracy. Hypnos and Hygeia were enthroned in awe and respect. As time went on this super-specialization was laughed at. Cicero makes Crassus observe that all arts are degraded by subdivision—"Do you suppose that in the days of the Coans and Hippocrates, there were special physicians—some for wounds and others again for the eyes?"

Before we assail the problem of the individual specialists in medicine and in science, let us look at some dangers. These I approach with a series of quotations. They must be viewed against the inevitability of specialism as facts accumulate and knowledge overmasters even the soundest intellect.

Here is what Ortega y Gasset has to say.

> It would be of great interest, and of greater utility than at first sight appears, to draw up the history of physical and biological sciences indicating the process of increasing *specialisation* in the work of the investigators. It would then be seen how, generation after generation, the scientist has been gradually restricted and confined into narrower fields of mental occupation. But this is not the important point that such a history would show, but rather the reverse side of the matter: how in each generation the scientist, through having to reduce the sphere of his labor, was progressively losing contact with other branches of science, with that integral interpretation of the universe which is the only thing deserving the names of science, culture, and European civilisation.
>
> What happens is that, enclosed within the narrowed limits of his visual field, he does actually succeed in discovering new facts and advancing the progress of the science which he hardly knows, and incidentally the encyclopedia of thought of which he is conscientiously ignorant. How has such a thing been possible, how is it still possible? For it is necessary to insist upon this extraordinary but undeniable fact: experimental science has progressed thanks in great part to the work of men astoundingly mediocre, and even less than mediocre. That is to say, modern science, the root and symbol of our actual civilisation, finds a place for the intellectually commonplace man and allows him to work therein with success. The reason for this lies in what is at the same time the great advantage and the gravest peril of the new science, and of the civilisation directed and represented by it, namely, mechanisation. A fair amount of the things that have to be done in physics or biology is mechanical work of the mind which can be done by anyone, or almost anyone. For the purpose of innumerable investigations it is possible to divide science into small sections, to enclose oneself in one of these, and to leave out of consideration all the rest. The solidity and exactitude of these methods allow of this temporary but quite real disarticulation of knowledge. The work is done under one of these methods as with a machine, and in order to obtain quite abundant results it is not even necessary to have rigorous notions of their meaning and foundations. In this way the majority of scientists help the general advance of science while shut up in the narrow cell of their laboratory, like the bee in the cell of its hive, or the turnspit in its wheel.

And the dangers Sherrington emphasizes —"When a single *specialization* becomes highly effective for its purpose, it tends to become so inextricably entangled in the circumstances of a particular place and time, that it can never be disentangled. That is, evolution can forget that places and times change, and that the surround is always becoming another surround. A specialization outlives its use. It can become a fatal encumbrance."

And we wind up the broad, general problem with Bernard Shaw's sardonic jibe, "No man can be a pure specialist without being in the strict sense an idiot."

And now specialization as a few physicians have seen its hazards. Austin Flint, in his striking posthumous work, "Medicine of the Future," warned:

"A dangerous tendency is to such a limitation to a specialty as will lead to withdrawal from the common interests of the profession. A medical specialist should not thereby, in his sentiments and conduct, be any the less a physician; the honor, dignity, and usefulness of the profession, as a whole, should be as sacred in his estimation as if he were not a specialist. If the effect of specialism be otherwise, alas for the medical profession of the future, as regards the respect of others and the self-respect of its members!"

MacNider emphasizes the proper background for all medical specialization in comments on a fine psychiatrist. "He was first a good doctor and second, erected on this sound bedrock of general medical understanding, came his specialization as psychiatrist."

The Source and Variety of Medical Specialties

One class of specialties in medical practice is those which have splintered off from general or internal medicine using diverse

ages as the line of cleavage. From conception to birth the obstetricians have staked out their claims. Immediately after birth, but not an instant sooner, the pediatrician rushes in and, sometimes distracted by the notion that children are not people, hangs on till some arbitrary milestone at the ill-defined boundary of puberty. Then the doctor who flourishes under the name internist (perhaps to be sure to avoid any implication of being a dermatologist) holds the victim until the gerontologist clutches him. Thus age is responsible for one general and three special fractions of health and disease.

Next a technique of therapy has chipped away a substantial group. Of these the most formidable group is the surgeons. Sometimes they are upset when I remind them that the name of their branch of medicine linguistically is the exact counterpart and has some of the same origin as chiropractor —the hand worker. While today the wise and well trained surgeon uses operative technique as only a part of his management of the sick, it is the essential part. Whenever today's physician feels the urge to chide his surgical colleagues, he should remember with gratitude how the barber surgeon kept alive the practical arts of caring for the sick while the physician, occasionally deigning to look at the urine but rarely at a patient, was lost in the webs of stratospheric speculation and confusion. Other specialties depending on a technique for their *raison d'être* outside the central body of medicine include Radiology, Physical Medicine, Psychoanalysis, and Anesthesiology.

Another group of specialists are separate from general medicine on a topographical basis. Each has set its fence around a piece of the body or several pieces connected by function or juxtaposition. Among these specialties are Dermatology, Ophthalmology, Otorhinolaryngology, Gynecology, Urology and Orthopedics.

And finally there are the specialists separated by ideology. These include Preventive Medicine, Public Health, Psychiatry, and I suppose we should put up a fence for administrators, both deans and hospital administrators, though many are not physicians by training or inclination.

If we want to divide by sex we can make a separate bundle for gynecology and obstetrics.

Within the ample domain of general or internal medicine sub-splintering goes on along the same lines. But where they are taught and practiced best cardiology, allergy, endocrinology, neurology, hematology and nutrition are wings of a single mansion and not outhouses.

Now I would like to quote from one of my favorite authors, myself:

"At a time when industry has found that pride in craft and contribution toward accomplishment is a stronger morale builder than wages or hours, we should see to it that the lesson is not lost on those who by design or by fate practice medicine in swarms. There is real danger that our patient may disappear as a person, John Smith, and become in fact that dry abstraction, the Common Man, whose conception is presided over by a conceptician, his birth attended by an obstetrician, his early days spent in the hands of a pediatrician, his burst into adult life in the hands of an adolescentist, and who during life is buffeted about among all the '-icians' and '-ists.' At length he begins to become unstrung under the careful guidance of a climactician. Finally the shriveling atrophy of old age is lubricated by the attention of a geriatrician until, bedeviled, bewildered, bemused, he falls exhausted off the end of the conveyor belt into the hands of the mortician. And all along the vast lockstep procession, teams and relays of specialists take turns at their posts on the day shift, the swing shift, and the graveyard shift, each to adjust one bolt, solder one wire, turn one screw, or take away bits of the wreckage; and the Common Man as he bounces along uneasily on his medical pilgrimage over the conveyor-belt road has no guide or companion unless he finds a personal physician."

What makes a budding doctor see
Which is his special, specialty?
Does just the wise one do his dernest
To pass the Boards as an internist?
Does surgery recruit great thinkers
Or manic, money grabbing tinkers?
Do those with fears and wire twists
Find solace as psychiatrists?
It is because their nostrils close
That some physicians pick the nose?
Are they frustrated engineers
Our orthopedic gadgetteers?
Do they reject frivolity
And people, in pathology?
Do those who're blind or cannot hear
Confine themselves to eye or ear?
Do those who did not work in classes
Seek a career in fitting glasses?
Are skin disease's devotees
Lured by short hours but longish fees?
With technics of some famed fan dancers
While veiling, I'll suggest the answers.

Analysis of motives for joining the exclusive clubs of the several specialties is full of danger. Only those sorry souls who are devoid of humor will reject this effort at needed therapeutic decompression of the pompous. Since they are not aware of any difference between flatus and afflatus, it doesn't matter. So at the risk of calling down on my head the powerful ire of my medical brethren in the splintered subunits of medicine, I proceed. Sir Robert Hutchinson, in a lecture to medical students once remarked, "Gentlemen, I have recently contracted matrimony. If Providence sees fit to bestow progeny and that progeny be the male sex, I shall one day have to consider his future. If he be a brilliant lad, far above normal, I shall make of him a physician. If he be merely normal, I shall make of him a surgeon. If he be slightly subnormal, I shall make of him a gynecologist. But Gentlemen, if he be absolutely mentally defective, I shall make of him an ear, nose and throat surgeon."

Why does anyone go into internal medicine? Lacking the organizing, unifying lines of the chemist, can it serve as an effective U. N. or supreme court for separate, sometimes hostile, often competitive, Balkanized principalities of the diverse specialties. I'm afraid internal medicine feeds the God-complex. My specialty favors the rise of the pontificator and the stuffed shirt. Unless tinctured by humility, it nourishes pomposity. Its hidden motto is "know it all." Impossibly demanding, its devotees may feel its extravagant demands without recognizing their own limitations. To the layman the internist may seem a happy blend of intellectual innocence and worldly wisdom, but the same layman, when ill, expects and often gets integrity and skill, but not as often as he desires, humane love.

A few comments about different specialists, I quote from a number of sources.

"Doctors may be divided roughly into physicians, who know a lot but can't do anything, and surgeons, who can do a great deal but don't know very much."

"Pediatricians enter their profession under the illusion that children are easier to handle than adults, and then spend their lives treating parents."

"The radiologist rejects the patient altogether, looking through him, not at him, in the fluoroscopic room, and studying his scant ectoplasmic shadows on the X-ray film. The retreat is that of the child and his picture book, away from reality."

"Frustrated engineers have an important place in certain medical specialties. The bridge builder becomes the bone setter, intent on stresses and struts, girders and girdles. As for the obstetrician he should have been a mining engineer, removing rich treasures from their hiding, doing best when he does least and erecting a fantastic mythology of turns, stresses, stages of labor which have little connection with reality but which divert the inventors and satisfactorily plague the undergraduate student. We must not forget the urologist, medicine's errant hydraulic engineer. He lives, bemused by tubes and pipes, pressures and streams, dams and conduits—happy when sphinctors are snapping off and on, but even merrier when he emulates the plumber with his multiplex armamentarium, if not his dilatory forgetfulness, in "getting the drains open." He measures his life in gold, urinary and mer-

cenary, with his main sentiments about sediments."

"Anesthetists and psychoanalysts share the curious similarity of having the patient in a helpless position, flat on his back and approaching him from the ancient position of ambush. Both induce sleep in one form or another." I can make little out of this useful observation.

"Neurologists may have gone astray trying to copy the engineers who gave us the complexities of the telephone and automatic switchboard. This clue might help us explain another hybrid, the worshipper at the shrine of cybernetics. We have now come to the really advanced stage of civilization when men can make a good living by going about proclaiming to fascinated audiences that the mind does not exist." I do not agree that merely uttering the word feedback permits one to assume that he has climbed the mental pinnacle called clarity and truth.

I have many more but, like all generalities, they are but partly true—emphasizing out of context.

I have made the assumption that we are mature enough to visualize our motives stripped bare of camouflage, without favor and without fear. We are the first generation raised by those who accepted the impulses Freudian psychoanalysis gave to psychiatry that personal responsibility was the bane leading us to trouble. The selfish needs, desires or wishes of the individual, the old Adam, must be gratified at all costs or the person would go off the track. Everyone else be damned. The model for social behavior is the apothesis of selfishness. But every mental institution is full of evidence to prove that complete self-centeredness is a most awkward organizing principle for such creatures as we are. A gain from insights developed along these lines is the realization that what we feel about others may reflect flaws within ourselves. Sensible persons now realize that their fears, hates and angers do not necessarily mean that the recipient is evil or wrong. Often we can say with truth, that

> The fault, dear Brutus, lies not in our stars,
> But in ourselves, that we are underlings.

Thus, from a surprising source, have come grounds for defending humility.

Conclusion

Most people go into medicine from a combination of practical and idealistic reasons. No one any longer drifts in. He can't be a doctor just because he wants to be one. The average person takes up medicine with no idea of consecrating his life but because he wants to earn a living in a useful and honorable profession. A physician can achieve nobility from an ambition no more exalted than of being a companion to his patients, a little taller, a little stronger, and a little wiser. The practice of medicine after a long apprenticeship puts one immediately into a position of respect and a chance to gain trust. It allows independence of judgment and action. It encourages the use of the intellect. If he achieves intellectual honesty, the physician is beholden to no man, no political group, no industrial machine. He may raise his family worthy of the approval of his fellow man. If he works harder and longer than the moneychanger, the rewards though different are proportionate. He may even find one of the was for reaching man's potential for natural dignity and honor.

Most of us engaging in the practice of a profession never analyze our reasons for selecting it. Some acknowledge accident and circumstance as the chief movers. To oversimplify a very complex problem, we become physicians from a mixture of motives compounded of altruism, curiosity and the search for power. Each is solving his own problems, satisfying his needs, and is driven by many forces never reaching the level of conscious motives.

Even the most cynical critic admits that a deep human impulse to help others has flourished in, and has made possible growth of, societies of people living together. At its best it takes on a religious aspect. At the other extreme it is no worse than the

wish to acquire merit. The virtue altruism still lives today without press agent or ballyhoo as a force leading youth into the profession of medicine. It may be declining. It is unfashionable, but still very important.

Curiosity, simple wonder at the marvelous and strange ways of nature, is another aspect of man which sets him apart from his fellow creatures. On it depends our understanding of the world about us. What forces are behind the mystery of generation, and growth, and life and death? What of the workings of our bodies, the meaning of health, the processes of disease? Contemporary education tends to stifle curiosity, and in our age of conformity the pioneer spirit of our forebears finds hardly any other outlet than in professions which depend for advance on the active probings of the inquiring mind. Research in medicine offers the thoughtful and curious person a challenge because of the infinitely various complexity of its problems. Its intellectual satisfactions are great. It permits one to deserve the ultimate accolade of a thoughtless age the brevet of "egghead."

The search for power is derived from all the ancient forces which enabled evolving man to thrive in a hostile world. In modern life, power usually is equated with things and money. Some is needed for survival. But power grows as an obsession. It may be an end in itself, without useful purpose. In medicine power may also satisfy a need to exercise authority to bolster a sagging or stunted ego. Most often it is the power of getting ahead of the Joneses. The prestige of material display in an age of childish delight in things has become a dominant drive in our machine oriented society. When power assumes the main or exclusive motivating force, medicine becomes just a business. Both physician and patient suffer. Think how amazed you would be if when you were sick you went to your physician and he told you that he personally had never cared anything about the art of medicine, that he never read current medical journals, paid no attention to the study of new treatments, and that he thought it really quite unimportant whether patients were sick or well, that he was really interested only in making a lot of money. What would you think of him?

The profession of medicine and its practice encompass the practical arts, basic science and applied science. The practical arts of medicine are nourished by altruism; the basic sciences are supported and embellished by curiosity; and the applied sciences live on power and feed it. Such motives govern our lives. In varying combinations they guide us in our choice of life work, and in doing it. The satisfactions of practicing a humane profession and the intellectual pleasures of exercising and sometimes satisfying curiosity are its real rewards. We must never lose them in a drive for power. For me, a physician, Life's great mystery is how people can be happy doing anything else.

A.M.A. ARCHIVES OF
INTERNAL MEDICINE

Surgical Management of Aortic Stenosis

An Evaluation of Techniques and Results

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Definition

While the term "aortic stenosis" appropriately might be applied to any one of several states in which the aorta or its first portion is congenitally hypoplastic or generally narrowed as the result of acquired disease, it usually is employed to designate a significant constriction of the orifice of the aortic valve itself. Congenital obstruction or narrowing of the left ventricular outflow tract, whether caused by a membrane, by a muscular shelf, or by simple hypoplasia, is referred to as subaortic stenosis, although in these same cases the valve itself also may be maldeveloped or hypoplastic. Anatomical aortic valvular stenosis usually implies stiffening of the leaflets or mutual cross adherence of their free margins with consequent reduction in the size of the valve aperture due to commissural obliteration.

Since aortic stenosis is one of the most common of the various valvular deformities produced by rheumatic fever, being second in frequency of occurrence only to mitral stenosis, and since, medically, it is a much more intractable and ultimately inevitably fatal lesion, efforts at its surgical alleviation would seem to be indicated more commonly and perhaps at an earlier stage in the course of this disease than is accepted generally in the management of mitral stenosis.

Historical Observations

It appears that Riverius [1] should be accredited for the first clear-cut description of calcareous aortic stenosis and for correlating the observed pathological changes with the clinical findings of a weak pulse and diminished peripheral arterial pulsations. Rayger,[2] Cowper,[3] and Vieussens [4] subsequently have discussed this entity. However, the brilliant description of Prof. John Baptist Morgagni,[5] in 1761, classically clarified the anatomical and pathophysiologic features of acquired aortic stenosis.

Embryology

The aortic valve, along with the pulmonary and the first portions of the corresponding great arteries, is developed during

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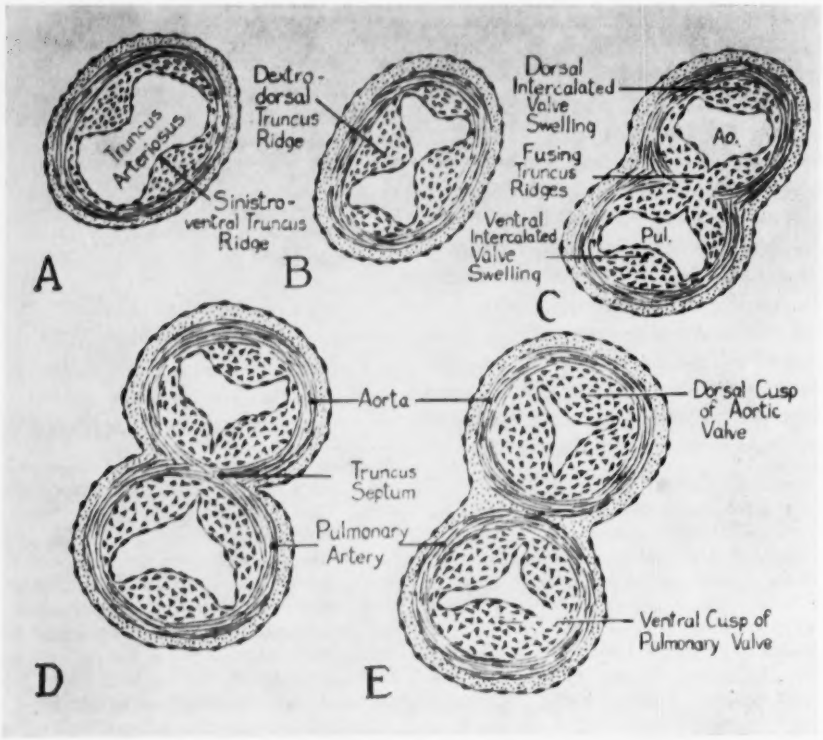
The research work required for the perfection of the surgical techniques described and for the development of the Friedland-Gemeinhardt extracorporeal circulatory apparatus was carried out in the laboratories of the Cardiovascular Institute of the Hahnemann Medical College and Hospital and was supported, in part, by a Grant from the National Heart Institute and by the Mary Bailey Foundation for Heart and Great Vessel Research.

the partitioning of the truncus arteriosus at about the sixth week of embryonic life. This process may be summarized as follows: The "truncus ridges," two apposed projections of "myxomatous" relatively acellular embryonic connective tissue, develop upon opposite sides within the lumen of the truncus arteriosus. They extend from the level of the sixth primitive aortic arch (which ultimately forms the pulmonary artery) to the level of the conus arteriosus, where they are continuous with the "conus ridges" which help to partition the ventricles. The truncus ridges run in a spiral fashion within the truncus, turning approximately 270 degrees in a counterclockwise direction (looking up from below). This is part of the mechanism of the "rotation" which gives the fully developed arteries the appearance of having been twisted about each other.

These ridges extend progressively more deeply out into the lumen of the truncus until they meet and fuse in the midline, thus dividing the lumen into two approximately equal-sized vascular channels. Later on, the truncus becomes separated anatomically to form the two great arterial trunks. In case of an unequal division of the truncus, one of the resulting vessels is significantly larger than the other.

The first sign of development of the semilunar valve cusps is seen at about the seventh week. The substance of the truncus ridges at the level of the junction of the truncus with the conus becomes thickened to form pads or cushions of embryonic connective tissue which extend out into the two, forming vascular lumina. At the same time, upon the opposite side of each of the incompletely separated vessels, another pad of "endo-

Fig. 1.—Successive stages in the partitioning of the truncus arteriosus and the development of the semilunar valves. Reproduced with permission from Kramer, T. C.: *Am. J. Anat.* (Philadelphia, Wistar Institute of Anatomy and Biology) 71:343, 1942.



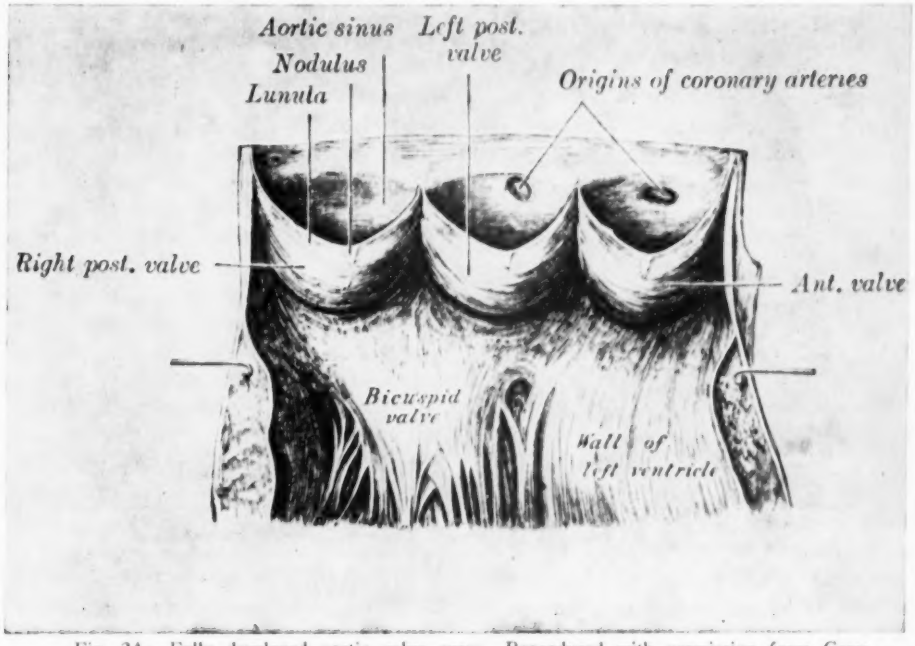
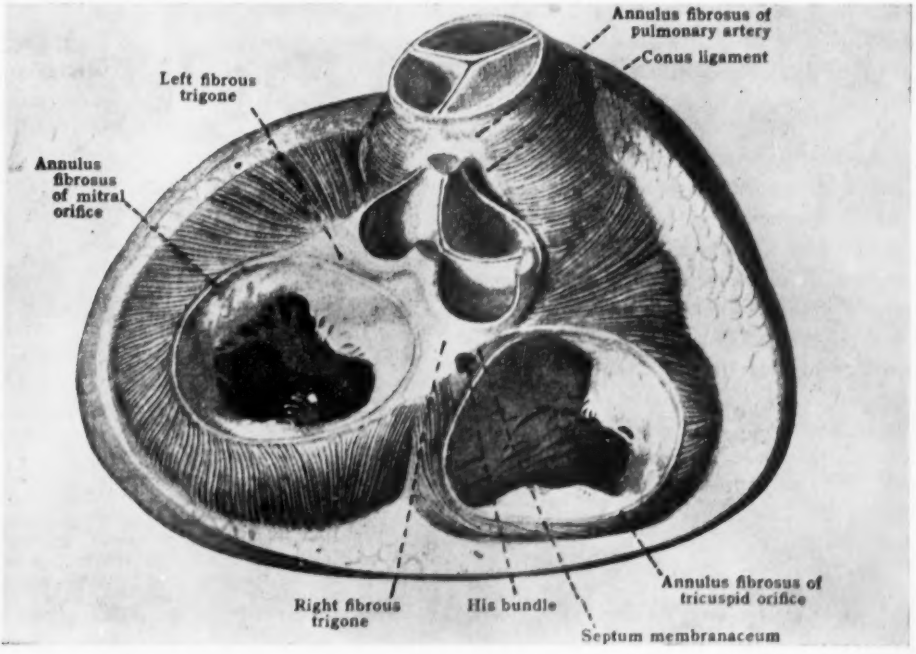


Fig. 2A.—Fully developed aortic valve cusps. Reproduced with permission from Gray, H.: Anatomy of the Human Body, Philadelphia, Lea & Febiger, 1954.

Fig. 2B.—Illustration depicting relative levels of semilunar valves in fully developed heart. Reproduced with permission from Tandler, J.: Lehrbuch der systematischen Anatomie, Berlin, Springer-Verlag, 1929, Vol. 3.



cardial cushion" tissue, called by Kramer [6] an "intercalated disc," develops and protrudes toward the swellings on the side of the ridges. These intercalated discs are destined to form, respectively, the posterior (noncoronary) cusp of the aortic valve and the anterior cusp of the pulmonary valve (BNA classification). By progressive thinning and molding and the development of collagenous and elastic fibers, three normally shaped cup-like semilunar cusps become formed within the lumen of each vessel (Fig. 1). Because of the method of development of these structures, the posterior commissure of the pulmonary valve permanently remains aligned with the anterior commissure of the aortic valve. This is true even though subsequent rotation causes the pulmonary valve and artery to come to lie to the left of the corresponding aortic structures. Furthermore, relatively greater growth of the conus segment of the right ventricle causes the pulmonary valve to lie at a higher (extracardiac) level than the aortic, which remains relatively deeply placed within the substance of the heart (Figs. 2A and 2B). These anatomical interrelationships between the structures of the semilunar valves are of great practical importance in the orientation of the cardiac surgeon.

Etiology of Aortic Stenosis

As has been suggested, aortic stenosis may be of congenital origin. It then may be part of a general hypoplasia of this region or the stenosis may be limited to the valve annulus or the leaflets alone. In the latter instance, it may take the form of funnel-like or cap-like developmental fusion of all commissures, similar to that seen commonly in congenital pulmonic stenosis, or there may be an absence or obliteration of one or two commissures with resultant transformation of the valve orifice, respectively, approximately into the diameter or the radius of the circular valve structure. Poststenotic dilatation of the first portion of the aorta is common in these congenital cases of valvular stenosis and is not infrequent in long-standing acquired aortic stenosis (Fig. 3). Poststenotic dilatation almost never is seen in subaortic stenosis.

The type of valvular deformity with nearly complete obliteration of one commissure due to congenital malformation or acquired disease has been considered to represent "bicuspid transformation" of the orifice.[7,8] However, such valves do not always present a serious or even a significant degree of stenosis physiologically. On the contrary, they may be associated with an appreciable, even a fatal, degree of aortic insufficiency. Such bicuspid aortic valvular deformities have been reported by Reifenstein, Levine, and Gross [9] to occur in about 40% of patients with coarctation of the aorta. The obliterated commissure frequently is represented by a rudimentary raphe dividing the larger of the cusps (usually the anterior one). The anterior commissure also is the one which most commonly becomes obliterated by the rheumatic process (Fig. 4).

Arteriosclerosis formerly [10,11] was believed to be the usual cause of aortic stenosis, and many adhere to this theory even today. However, a larger number of authors [12-15]

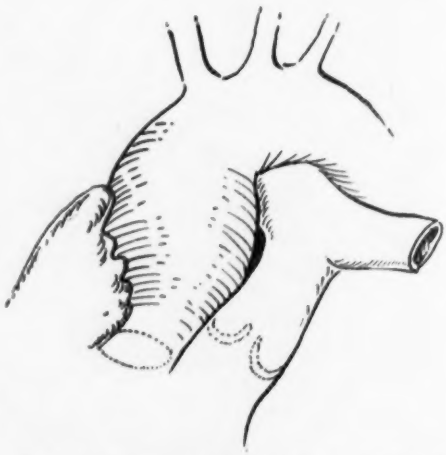


Fig. 3.—Poststenotic dilatation of ascending aorta. This is a characteristic finding in congenital aortic valvular stenosis, but also is seen not infrequently in long-standing acquired aortic stenosis. Reproduced with permission from Bailey, C. P.: Surgery of the Heart, Philadelphia, Lea & Febiger, 1955, p. 753.

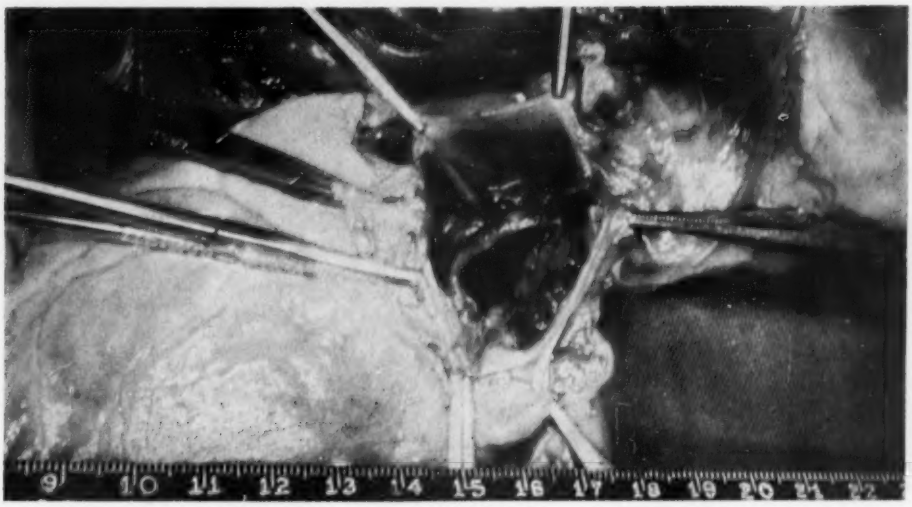


Fig. 4.—Congenital stenosis of the aortic valve. Note raphe representing location of rudimentary anterior commissure in a patient with coexisting aortic coarctation. Resultant bicuspid valve also was incompetent. Reproduced with permission from Bailey, C. P., et al.: *J. Thoracic Surg.* (St. Louis, C. V. Mosby Company) 31:375, 1956.

now accept the rheumatic state as the most frequent etiologic agent. We agree with this concept, especially in view of the fact that coexisting, indubitably rheumatic lesions of the mitral valve are seen in approximately half of all patients with aortic stenosis. And, the pattern of aortic pathology seen in these combined cases is identical with that seen in most instances of isolated aortic stenosis. Hence, these latter presumably are of rheumatic origin also. Calcification is so common in rheumatic mitral stenosis (39.4% in our cases) that its somewhat greater incidence (approximately 90%) in stenotic lesions of the aortic valve, one which is subjected to much greater functional trauma and stress, is not surprising. Certainly the higher incidence of calcification of this valve would not tend to exclude a rheumatic etiology of aortic stenosis. Possibly the longer period of time required for the full development of severe stenotic aortic lesions may account for this higher incidence of calcification.

We have described [7,16,17] a type of aortic stenosis which we believe to be of arteriosclerotic origin, in which commissural obliteration does not take place. The leaflets which anatomically are nondeformed grossly become stiffened by calcific infiltration and are seen in a position of incomplete closure. In such cases, a certain amount of valvular insufficiency must exist as well as a large degree of impedance to forward blood flow.

Acute or subacute bacterial infection of an aortic valve previously deformed by the rheumatic state or by congenital malformation may be cured now that effective antibiotic measures are available. The vegetations and ulcerations characteristic of these lesions may heal (by fibrosis), with resulting further deformation of the valve. However, since the over-all structural abnormality tends to follow the pattern of the original pathology, it is likely to be responsive to surgical measures appropriate for those lesions.

Pathogenesis of Rheumatic Aortic Stenosis

In the earliest phases of rheumatic aortic valvulitis, minute vegetations, really firmly attached tiny fibrinous thrombi, appear upon the free margins and the lunulae (zones of leaflet approximation) of the aortic valve cusps. This site of localization seems, at least in part, to be related to the incessantly

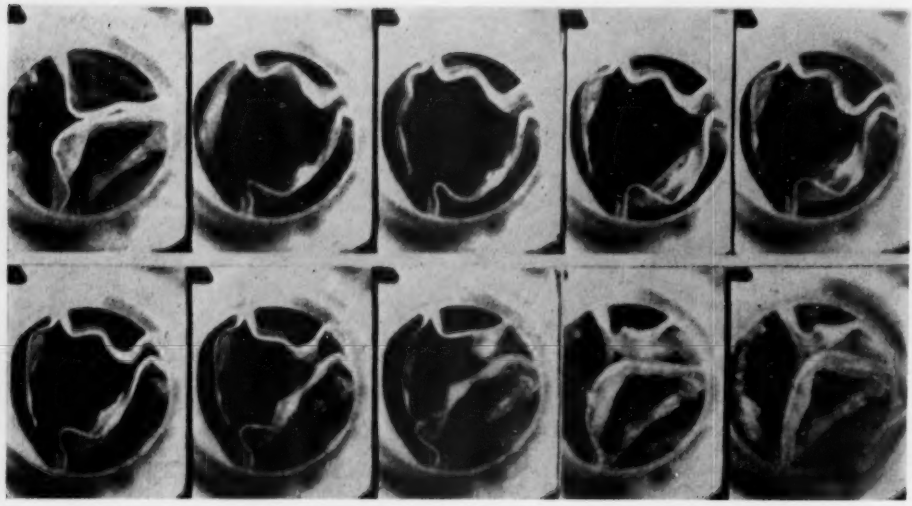


Fig. 5.—Successive steps in the opening and closing of the aortic valve. Note that the effective passageway is a triangular one, as postulated by da Vinci four centuries ago. Reproduced with permission from McMillan, I. K. R.: *Brit. Heart J.* (London, British Medical Association) 17:56, 1955.

repeated trauma of valve opening and closing. The roughening of the leaflet surfaces produces a turbulence in the flow of blood through the aortic passageway. This aperture has been described by da Vinci,[18] in 1513, and demonstrated by McMillan,[19] in 1955, to be roughly triangular in outline during systole (Fig. 5). As a result of this turbulence of blood flow, and perhaps also for chemical or biologic reasons, platelet and fibrinous deposition tends to take place upon these roughened surfaces of the valve, in spite of the rapidity of blood flow. A less amount of such fibrinous deposition may take place generally upon the other surfaces of the valve, especially upon the aortic aspect and also within the sinuses of Valsalva (perhaps because of relative stagnation of flow within these vascular recesses). In the region of the commissures, the fibrinous exudate become heaped up, tending to "bridge" the angles formed by the proximity of the free margins of the cusps.

In time, fibroblastic invasion of the surface exudate, as well as of the vegetations themselves, organizes it into a thin layer of fibrous connective tissue with the bulk of the partially organized vegetations protruding through it. This results in an increase in the substance of the valve and in thickening which diminishes its flexibility. Successive layers of such exudate may become deposited upon the leaflets. This culminates in the accretion of differentially organized lamellae of scar tissue upon the respective surfaces of each cusp. Apparently this process must continue at least until the fibrosed remnants of the original vegetations are buried completely.

Simultaneously, organization of that portion of the exudate which "bridges" the valve commissures leads to cross adherence of the adjacent portions of the valve edges at their aortic wall attachment. This partial binding together of the leaflet extremities results essentially in moving the effective valve commissures somewhat closer to the midline. A subsequent deposition of fibrin may bring about another bridging of each new "commissure" with exudate. Again, organization at each angle must produce further valvular cross adherence. This process, if symmetric in all commissures, logically may advance until the formerly large aortic valve aperture has been reduced to

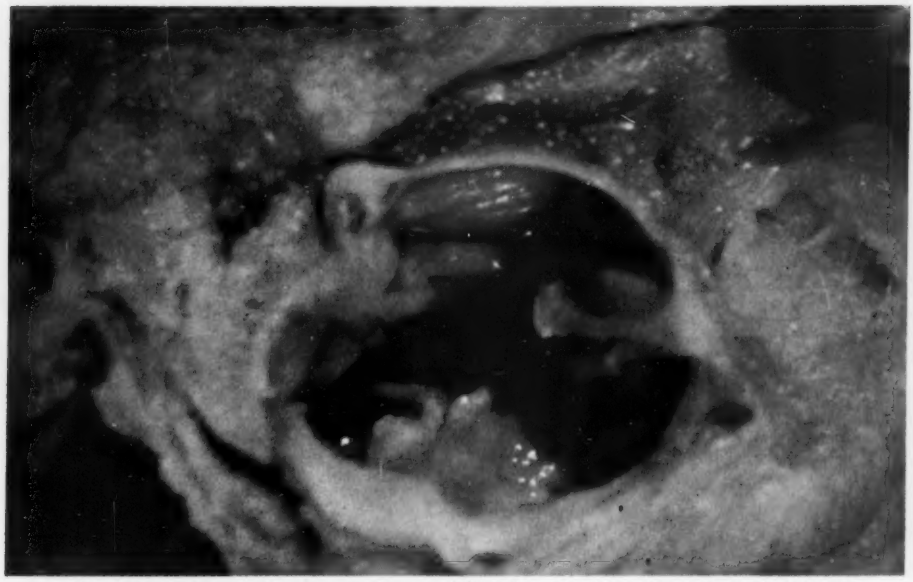
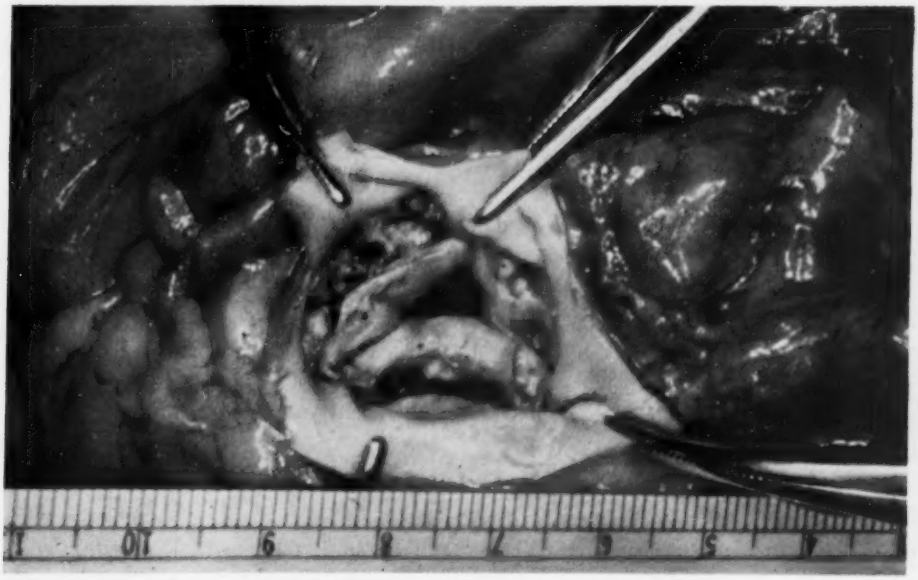


Fig. 6A.—Early stage of commissural obliteration in rheumatic aortic valvulitis. Reproduced with permission from Bailey, C. P., et al.: *J. Thoracic Surg.* (St. Louis, C. V. Mosby Company) 31:375, 1956.

a tiny central triangular opening (Figs. 6A and 6B).

Should the process of centripetally progressive commissural adherence be asymmetric, either one or two commissures may become obliterated totally, the remaining being completely or partially unfused. In many instances, obliteration of a single

Fig. 6.B.—Late stage of symmetrical commissural fusion of aortic valve cusps producing a significant stenosis and a less significant degree of regurgitation. Note calcification of the aortic sinuses as well as of the valve margins. Reproduced with permission from Larzelere, H. B., and Bailey, C. P.: *J. Thoracic Surg.* (St. Louis, C. V. Mosby Company) 26:1953.



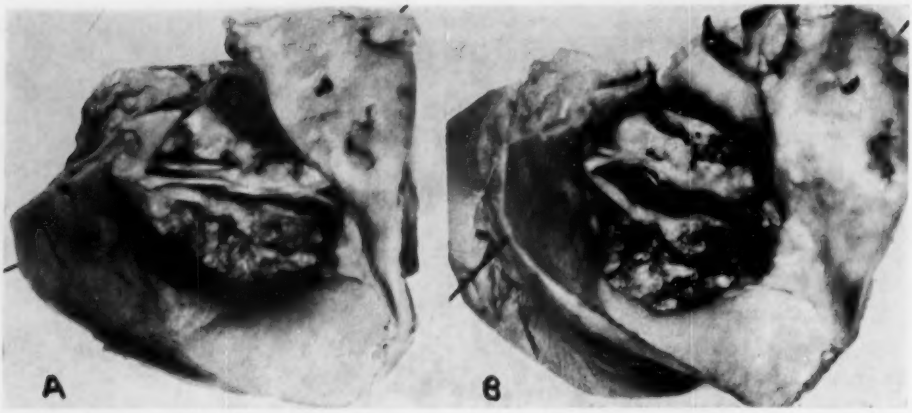


Fig. 7.—A, bicuspid transformation of the aortic valve due to acquired aortic stenosis, with asymmetric obliteration of the commissures. Note calcification. Only one commissure really was partially open. B, same valve with the rigid leaflets forced apart by handle of knife blade. This could be accomplished only by splitting apart one fused commissure. Reproduced with permission from Bailey, C. P.: Surgery of the Heart, Philadelphia, Lea & Febiger, 1955, p. 759.

commissure leads to bicuspid transformation of the valve (Figs. 7A and 7B).

Magarey[20,21] seems to imply that the corresponding process affecting the mitral valve, once initiated, may become essentially self-perpetuating, terminating only when the valvular obstruction becomes lethal. If this concept be true, one would expect it to be equally appropriate to a stenosing rheumatic lesion of the aortic valve. Universally, it is believed that recurrence of the rheumatic state will reinstitute or exacerbate the course of such a stenosing process.

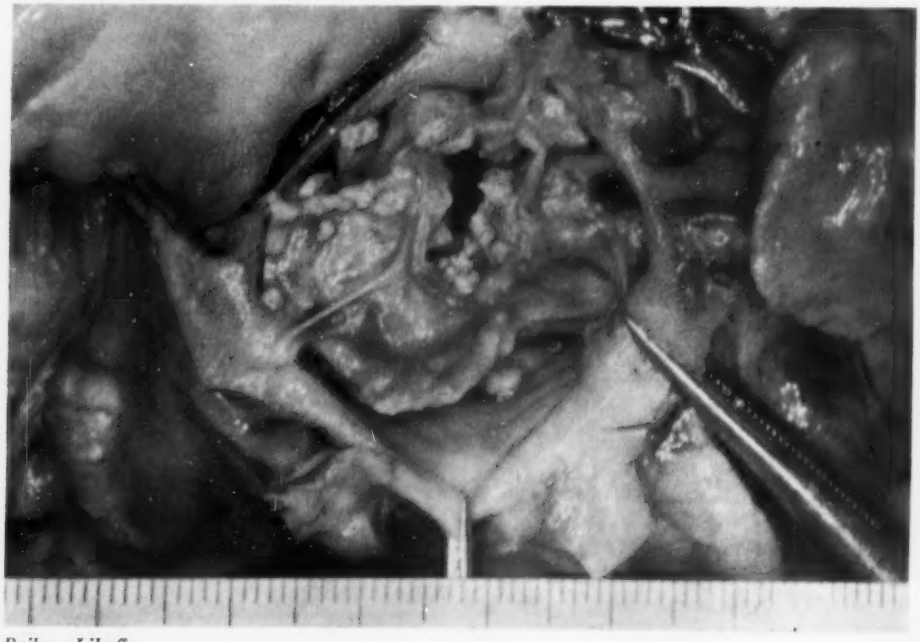
Inevitably, in time, the newly acquired fibrous tissue upon the surfaces of the valve must exhibit its inherent tendency toward contraction. This may take place in such a fashion as to shorten the length of the original arcuate free margin of the valve and thus to bring about its retraction toward the aortic wall. In rheumatic aortic stenosis, the fundi of the cusps become shallower than normal, presumably owing to the type of centrifugal contraction of such scar tissue elaborated upon the surfaces of the leaflets. This "line of pull" of contracting fibrous tissue would seem to tend to create an element of aortic insufficiency. And, this effect of intrinsic rheumatic distortion of the aortic valve is seen not infrequently (Fig. 8).

However, the combined contraction of the joined tricuspid segments of heavy scar tissue formed about the free margin of a valve orifice which has been reduced in size by the previously described process of commissural obliteration must act to constrict the diminished aperture still further. Thus, a counterbalancing tendency toward "sphincteric" obliteration of the remaining valve orifice usually overcomes the tendency toward leaflet retraction and consequently tends to inhibit the development of any element of insufficiency. This explains the much greater incidence of valvular stenosis than of regurgitation in rheumatic patients, and the observed propensity toward clinical preponderance of the stenotic element in most instances of combined aortic stenosis and regurgitation. There is, however, a type of aortic insufficiency, due to rheumatic disease, which appears to be due almost entirely to weakening and dilatation of the annulus, the leaflets themselves suffering no deformation.

With the passage of time, probably in part due to the relative immobility of the thickened leaflets, late degenerative changes may develop within the distorted valve. Of these, the most prominent is calcification. It is presumed that the excessive trauma

Fig. 8.—Acquired (rheumatic) aortic insufficiency (with some insignificant element of stenosis) due to preponderant tendency of fibrosed leaflets to retract. Reproduced with permission from Bailey, C. P.: Surgery of the Heart, Philadelphia, Lea & Febiger, 1955, p. 758.

Fig. 9.—Extreme calcification of aortic valve with easily dislodged excrescences. These are the source of most embolic complications which attend surgical attacks upon the aortic valve by either of the closed methods.



and stress to which the aortic valve normally is subject may account for the very high incidence of calcification of the leaflets (approximately 90%) observed in aortic stenosis. This calcification may extend beyond the surface of the leaflets, and sometimes becomes heaped up into "stalagmites" which extend for a distance up the aortic wall (Fig. 9).

Most frequently, the calcification seems to become localized within or upon the obliterated commissures. However, it may involve only the free margins of the valve. And, sometimes it may be limited to the sinuses of Valsalva, where its clinical significance is slight (since it then does not prevent opening of the aortic valve to its full natural or remaining triangular aperture) (Fig. 6B). In more advanced cases, the calcification may involve the entire aortic valve ring. Or, the entire valve may become converted essentially into a "rock pile" or "volcano." When a bicuspid valve becomes extensively calcified, it may develop a "clam-shell-like" structure (Fig. 7). In rare instances, fortuitously located heaped-up masses of calcification may tend to block or to impede the entrance of aortic blood into the coronary ostia.

The aortic ring may become narrowed or restricted somewhat due to an intrinsic rheumatic involvement of the aortic annulus fibrosus such as may be seen in the atrioventricular valves (aortic "ring" lesion). However, such narrowing of the ring is observed relatively rarely and by itself apparently "never" produces a serious impedance to transvalvular blood flow. The first portion of the extracardiac aorta is likely to exhibit "poststenotic" dilatation in long-standing cases, and this may present a dramatic contrast to the narrowed annular region (Fig. 3).

In "pure" aortic stenosis, the left ventricle characteristically undergoes a "concentric" type of hypertrophy—thickening of its walls without significant increase in the size of the chamber. Even though the walls of the left ventricle may become as much as 1 in. (2.5 cm.) in thickness, it may be hard to detect an increase in the over-all size or significant distortion of the radiographic outline of the heart. However, when exhaustion and heart failure supervene, or when significant aortic regurgitation coexists, a boot-like contour of the cardiac shadow will develop (Figs. 10A, 10B, and 10C).

In long-standing isolated aortic stenosis, the left ventricle tends to become soft and friable, apparently undergoing an unusual form of myocardial degeneration which may be related to the long-continued "isometric type" of contraction and overwork in the presence of relative coronary insufficiency. Surgically, this is important in that some of these ventricles are found to be so soft that hemostatic sutures placed in their walls will tend gradually to "saw" or cut through the contracting tissue. In our experience, this has resulted in fatal hemorrhage, both in the operating room and subsequently.

Furthermore, such an obstructed ventricle may exhibit exquisite irritability and develop runs of ventricular extrasystoles at the slightest mechanical stimulus, such as

Fig. 10A.—Concentric hypertrophy of the left ventricle with relatively slight chamber enlargement in "pure" rheumatic aortic stenosis.

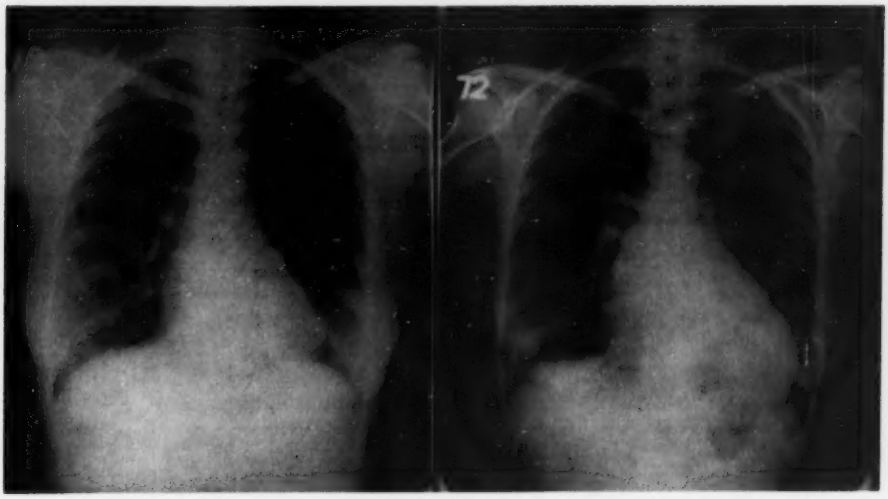


Fig. 10B.—Roentgenograms of same patient as in Figure 10A taken, respectively, four years and two weeks prior to her death. Note lack of left ventricular predominance even in the presence of considerable over-all cardiac enlargement.

touching or suturing. At times, such an arrhythmia may progress through a state of ventricular tachycardia to one of ventricular fibrillation. The latter condition appears, nearly always, to be recalcitrant to the usual appropriate defibrillatory measures unless the aortic obstruction can be (and is) relieved rapidly.

Fig. 10C.—Boot-like configuration of cardiac shadow due to left ventricular dilatation (and hypertrophy) in a patient with coexisting rheumatic aortic stenosis and insufficiency. Reproduced with permission from Bailey, C. P.: Surgery of the Heart, Philadelphia, Lea & Febiger, 1955, p. 763.

Pathophysiology

When the size of the aortic valve orifice is reduced seriously, an elevation in the intraventricular systolic pressure is necessary to sustain normal blood flow through the narrowed opening. Thus, a pressure gradient becomes established between the left ventricle and the aorta.

In general, the height of the pressure gradient developed is proportional to the caliber of the channel between the ventricle and the aorta (the magnitude of the stenosis). However, the stroke output and, hence, the work capacity of the left ventricle are equally determinative. If the area of the aortic orifice is reduced below a point variously estimated at from 50% to 25% of normal, a very marked pressure gradient is required to expel a normal quantity of blood into the aorta. The increased systolic intraventricular pressure which strives to maintain a normal stroke volume in spite of the hindrance to outflow appears to be the fundamental dynamic effect of aortic stenosis.

A. Left Ventricular Response.—The ability of the myocardium to develop greater intraventricular pressures and to sustain a rise in gradient depends upon contractile tension. According to Starling's experiments,[22] contractile tension improves as the diastolic length of the myocardial fibers increases. However, this relation does not apply once the muscle becomes "overstretched." The law of Laplace[23] enters into these considerations, since it implies that greater tension is required to develop a given systolic pressure when the initial length of the myocardial fibers is increased.

Thus, if the diastolic length of the cardiac muscle fiber increases excessively, contractile tension fails at the very time when it is most urgently required to maintain the essential intraventricular systolic pressure. These interacting mechanisms indicate that myocardial hypertrophy, not dilatation, is the most efficient response to the increased pressure load of aortic stenosis, and, indeed, in the early stages of the disease, the left ventricle is observed to react in this manner. Roentgenographically, the heart size usually is not greatly increased, and the left border appears rounded, presenting the contour of concentric hypertrophy (Fig. 10A).

In the later stages of aortic stenosis, the cardiac muscle suffers a loss of contractility, and the left ventricle enlarges grossly (Fig. 10B). Greater myocardial tension then is required to sustain effective ventricular pressures. This functional burden imposes a grave demand for energy output, and, with time, failure of the left ventricle must ensue.

B. Effect on Coronary Blood Flow.—The elevated intraventricular pressure in aortic stenosis exceeds the pressure within the coronary arteries, and thus impedes the filling of these vessels during systole. In addition, the hypertrophy and overwork of the left ventricular muscle which accompanies significant aortic valve obstruction not only increases its nutritional requirements, but also lengthens the diffusion distance between coronary blood supply and the active cell. These factors in combination account for the relative degree of myocardial ischemia which usually develops. Coronary arterial insufficiency unquestionably contributes to the loss of muscle contractility which is observed in the advanced stages of this lesion. In many instances, the subjective manifestation of this deficiency in blood supply (anginal syndrome) dominates the entire clinical pattern.

C. Effect on Cerebral Blood Flow.—Under conditions either of rest or exercise, the stroke volume may fall in aortic stenosis. The transient resultant inadequate cardiac output probably arises from the interrelated factors which regulate the ability of the myocardium to develop an effective intraventricular systolic pressure. More remotely, it may be secondary to momentary ventricular arrhythmia. Since the cerebral circulation is exceptionally sensitive to variations in systolic output, vertigo and syncope are common components of the clinical manifestations of the disease.

The Development of the Surgical Treatment of Aortic Stenosis

The surgical approach to aortic stenosis has matured through the same hesitancies and trials which marked the development of commissurotomy for mitral stenosis. The principle that the orifice of a stenotic valve can be expanded safely only by separating the fused leaflets along the lines of natural anatomical cleavage had not been acknowledged when Smithy, in 1947,[24] planned to relieve aortic obstruction by punching out a portion of the valve.[25]

Even after the principle of commissurotomy had become established,[26] the inaccessibility of the aortic valve remained a deterrent to a proper surgical approach. Indeed, a safe portal to the valve seemed so improbable that efforts were directed toward bypassing the obstruction. Similar misgivings and technical escapes had been experienced and practiced for mitral stenosis.[26,27] In our laboratories, in 1950,[28] unsuccessful attempts were made to bypass the

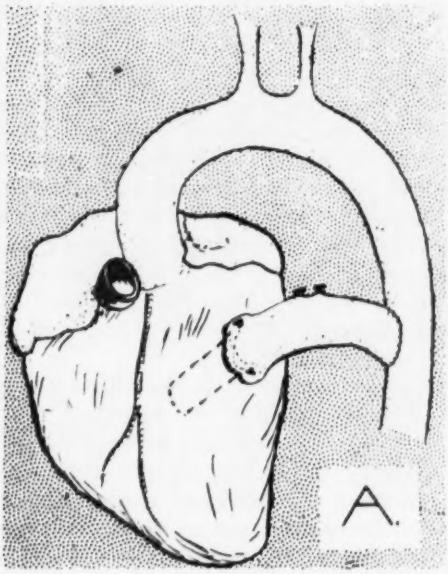


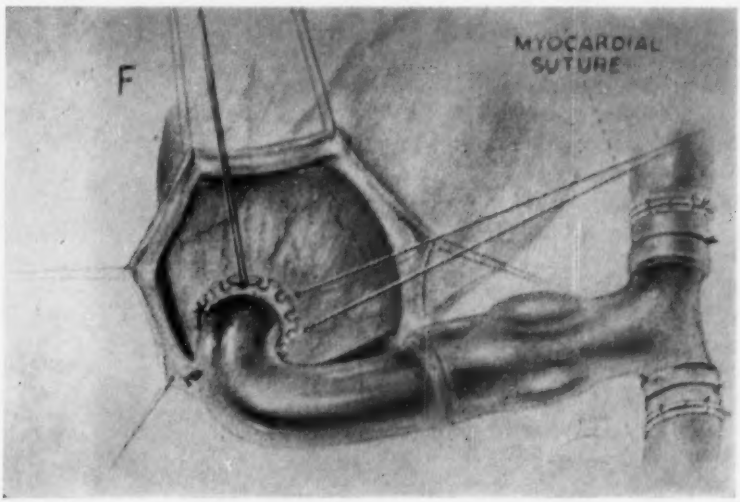
Fig. 11A.—Experimental attempt at bypass of stenotic aortic valve using double valve-containing aortic homograft. Reproduced with permission from Bailey, C. P., et al.: *J. Thoracic Surg.* (St. Louis, C. V. Mosby Company) 20:516, 1950.

aortic valve by using a double-segment aortic homograft containing a normal valve which was placed between the lumina of the left ventricle and the descending aorta (Fig. 11A). Recently Sarnoff and Case[29] have produced a similar shunt in dogs, using a modification of the Hufnagle valve which is inserted into the apex of the left ventricle (Fig. 11B).

The direct approach to the problem of aortic stenosis originated with the first efforts to create suitable portals to the valve. In 1950, one of us (C. P. B.) inserted an instrument with two retractable cutting blades into the left ventricle through its muscular wall and divided the fused valve orifice[28] by a technique similar to that employed by Brock[30] and Potts[31] for pulmonary valvulotomy. Dynamic aortic regurgitation resulted (fatally). This experience seemed to establish the need for an instrument capable of separating aortic commissural fusion by blunt disruptive pressure alone, rather than by incision. It also substantiated the practicability of using the left ventricle as an avenue of approach to the aortic valve.

The first instrument designed to separate the aortic commissures by blunt pressure utilized the right common carotid artery as the entrance passage to the aortic lumen.[28] Initially "successful" in clinical application in April, 1950, this method was abandoned

Fig. 11B.—Similar attempt to bypass aortic valve using modified plastic valve of Hufnagel. Reproduced with permission from Sarnoff and Case: Henry Ford Hospital's International Symposium on Cardiovascular Surgery, Philadelphia, W. B. Saunders Company, 1955.



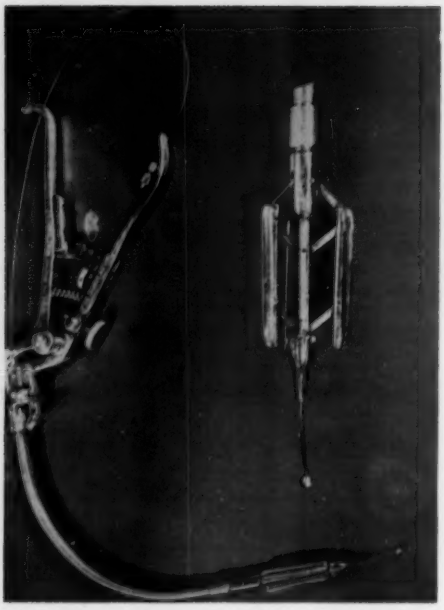


Fig. 12A.—Triradiate dilator developed by Donaldson for performance of aortic commissurotomy by the transventricular route. Since then a modified dilator employing a similar principle has been developed for the transaortic route. Reproduced with permission from Henry Ford Hospital's International Symposium on Cardiovascular Surgery, Philadelphia, W. B. Saunders Company, 1955.

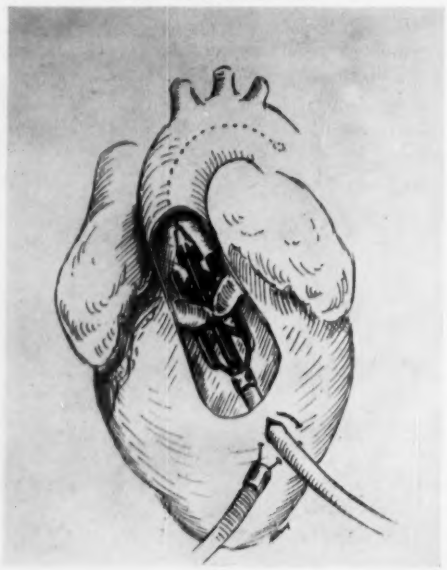
subsequently when insurmountable difficulties were experienced in one patient in an attempt to guide the dilator through an eccentrically located valve orifice.

In 1952, a more useful dilator finally was developed under our direction by Major J. Shearman Donaldson, of Chatham, N. J. This was designed to enter the heart through an incision made in the muscular wall of the left ventricle and to engage the aortic valve from below (Figs. 12A and 12B). The head of this instrument is triangular on cross section and turns freely upon the shaft, thus tending automatically to adjust to any residual triangularity of the valve orifice. The wedge-like blades are separated by compression of the hand grips and exert forceful pressure against the strategic points of valve fusion (obliterated commissures) (Fig. 13).

The successful clinical application of the instrument [16] established a reasonable technique for the surgical modification of aortic stenois. However, this method, termed "transventricular aortic commissurotomy," violates certain basic principles of closed cardiac surgery. Essentially it necessitates direct trauma to the hypertrophied and often extremely irritable myocardium of the left ventricle, commits the surgeon to a preselected degree of expansion of the aortic valve orifice without prior palpatory exploration, and prevents him from directing or limiting the action of the dilator by digital control at the very moment of its critical application.

In the interest of avoiding these patent faults, the technique of transaortic commissurotomy was developed.[16,17] This procedure avoids myocardial injury by permitting the surgeon to insert his finger directly into the lumen of the aorta through an artificially created pouch, thus enabling him to reach the valve without unusual blood loss. The commissures then are split or incised under digital guidance (Figs. 14A, 14B, and 14C).

Fig. 12B.—Diagrammatic representation of Donaldson type dilator in use. Free rotatory mechanism at junction of head with shaft permits automatic adjustment of angles of dilator to any residual triangularity of the valve orifice. Reproduced with permission from Bailey, C. P., et al.: *J. Internat. Coll. Surgeons* (Chicago, International College of Surgeons) 20:393, 1953.



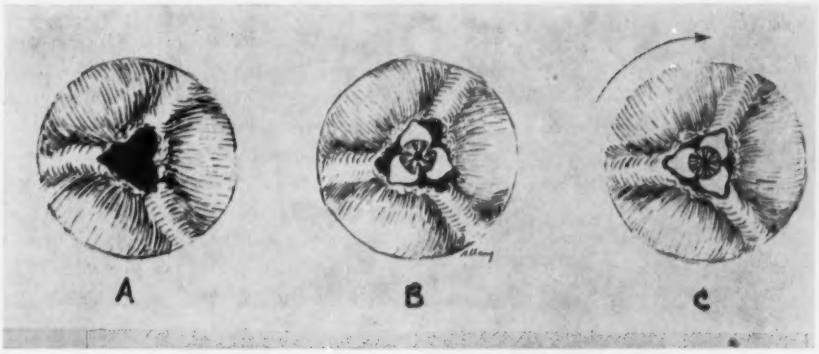


Fig. 13.—A, diagrammatic representation of diminutive triangular aortic stenotic orifice due to symmetrical obliteration of the commissures. B, representation of fortuitous improper alignment of triradiate dilator head within the aortic orifice. C, free rotation of the head upon the dilator shaft automatically realigns its triangular cross section with the outline of the triangular valve orifice. Spreading of the triradiate blades now will apply disruptive pressure directly against the central extremities of the lines of commissural fusion. Reproduced with permission from Larzelere, H. B., and Bailey, C. P.: *J. Thoracic Surg.* (St. Louis, C. V. Mosby Company) 26:31, 1953.

While this method of attack in many instances has enabled the surgeon to accomplish great amelioration of the physiological aberrations associated with aortic stenosis, this valve more frequently than any other is afflicted by morphologic changes which may offer critical barriers to the successful conclusion of corrective surgery. Although transaortic commissurotomy represented a distinct advance, it did not permit the surgeon to overcome all the handicaps imposed by the structural abnormalities of the valve. Among these, extensive calcification and extreme rigidity of the leaflets are the more important.

Fig. 14A.—Transarterial digital approach to the aortic valve, using a pouch of pericardium or plastic fabric sutured to an excluded portion of the ascending aorta.

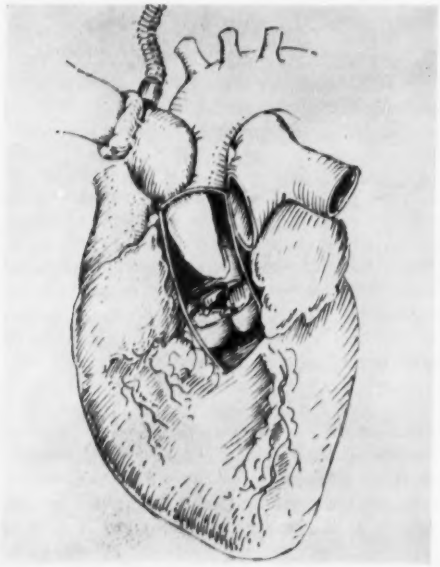


Fig. 14B.—Digitally guided division of the fused valve commissures by a guillotine knife inserted through the pouch.

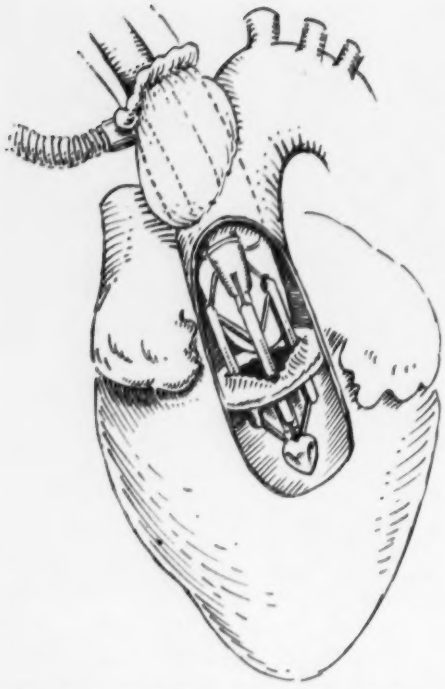


Fig. 14C.—Digitally guided transaortic dilatation of the valve, using Donaldson dilator.

Accordingly, with the recent development of practical instruments for circulatory bypass (artificial heart-lung apparatus) and the perfection of methods for the performance of surgery upon the interior of the opened heart, it was logical to apply such techniques to the correction of aortic valve obstruction.

Lewis [32] employed hypothermia to permit surgery upon the aortic valve under direct vision on Dec. 2, 1955. Lillehei [33] was the first to correlate the function of the heart-lung machine with the fundamental observations of Blanco, Adam, and Fernandez [34] that coronary circulation could be sustained when the aorta was opened by retrograde perfusion of the myocardial capillary bed through the coronary sinus. Utilizing a bypass apparatus and this perfusion technique, he successfully "corrected" calcific aortic stenosis in the opened heart on Jan. 31, 1956.

Shortly thereafter, a success was obtained (April 12, 1956) [35] in our clinic, using a similar method upon a patient with congenital aortic stenosis. On the same day Morrow [36] performed an open aortic commissurotomy, using a heart-lung bypass, but without retrograde perfusion of the coronary sinus. Since then 10 patients with acquired calcific aortic stenosis have been operated on in this manner in our clinic with 9 survivals and 1 death. While the open attack involves many additional problems of a practical nature, it does permit a technically more perfect aortic commissurotomy to be accomplished.

Therefore, there exist at the present time three distinctive individual methods for the surgical modification of aortic stenosis or closely allied obstructions at the outflow tract of the left ventricle. Two of the techniques, transventricular and transaortic commissurotomy, are practiced in the closed heart and have been established sufficiently long to undergo statistical evaluation. The third is a most recent procedure which involves the many principles and problems associated with open heart surgery as well as those related to mechanical mobilization of the valve (Fig. 15A and 15B).

The purpose of this communication is the analysis of our clinical experience with each of these methods. In this manner, their fundamental strengths and weaknesses may be appraised in terms of operative mortality and morbidity as well as of symptomatic and physiologic response.

Material

While various efforts have been made to modify aortic stenosis surgically in more than 450 patients by the individual members of our staff, it was felt that the results obtained in those patients with associated significant or preponderant regurgitant valvular disease and in those operated in hospitals where we do not work consistently were not pertinent to this discussion.

In the interval from April 4, 1952, to Feb. 1, 1956, two hundred eighty-seven patients with major aortic stenosis have been treated surgically by closed heart techniques at the Hahnemann Hospital in Philadelphia. They have been divided into two categories. Group I includes patients subjected to aortic commissurotomy for aortic stenosis alone or in combination with other

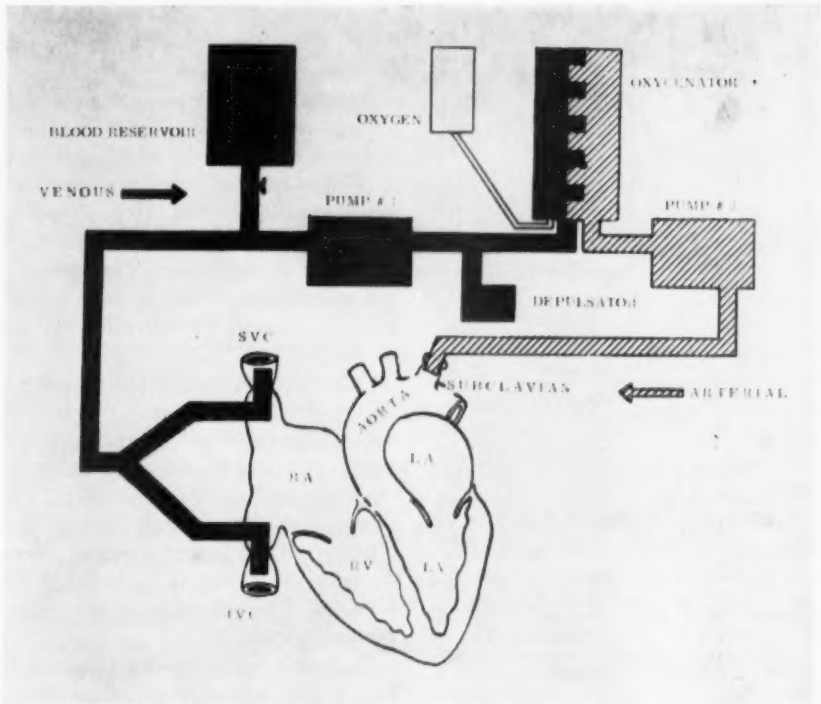


Fig. 15A.—Diagrammatic illustration of bypass method for direct vision commissurotomy of the aortic valve, using the Friedland-Gemeinhardt Oxygenator and the Sigmamotor Pump. Reproduced with permission from Bailey, C. P., and Gilman, R. A.: Clinical Experience with the Friedland-Gemeinhardt Oxygenator, presented at Spring Meeting of the American Society for Artificial Internal Organs, Atlantic City, N. J., April 16, 1956.

adynamic, physiologically "insignificant" lesions, mainly minor degrees of aortic regurgitation. Group II consists of patients who required simultaneous aortic and mitral commissurotomies for coexisting stenosis of both valves either alone or in combination with other minor valve lesions (Tables 1 and 2).

Since April 12, 1956, eleven patients have been operated on by the open method, using a heart-lung bypass and retrograde perfusion of the coronary sinus. This group is considered as a unit and evaluated independently.

Clinical Manifestations (Table 3)

In Group I patients dyspnea was the earliest, most frequent symptom encountered (86.5%). Acute paroxysmal dyspnea with pulmonary edema, however, was less common, occurring only in 21.3% of the patients. Fatigue was closely associated with dyspnea and appeared in 78.2% of the group. The pain of coronary artery insufficiency was the third most common complaint (48.2%). It never was encountered as the only manifestation of aortic stenosis. The onset, frequency, and severity of the angina could not be related to the age of the patient.

Vertigo and syncope were significant complaints in approximately 30% of the patients in this group. There was no specific pattern to the attacks of unconsciousness. They were multiple, with varying intervals separating the attacks, and for the most part were without relation to definite types of stress.

Peripheral edema and other manifestations of congestive failure either alone or in combination developed in 30% of the patients.

The average duration of each major symptom in the patients comprising Group I was less than two years.

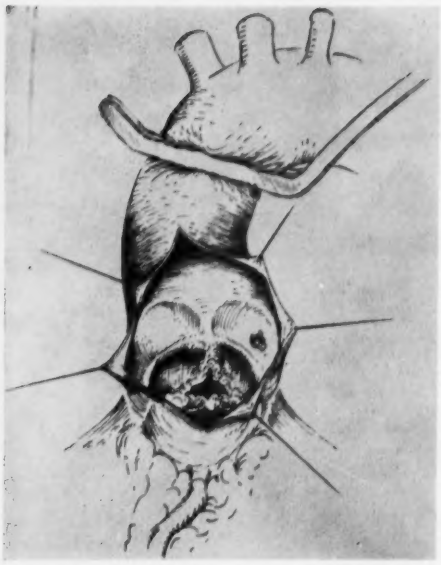


Fig. 15B.—Front view of interior of ascending aorta as seen during open commissurotomy for aortic stenosis. With special scissors, a critically accurate separation of the commissures becomes possible. Any loosely attached or detached calcific particles may be extracted mechanically.

The differences in the symptomatic manifestations between the patients in Group I and II were striking. Again dyspnea and and fatigue were the commonest complaints. Angina, vertigo, and syncope occurred less commonly in Group II patients. Paroxysmal dyspnea and edema were more frequent. The average duration of the major complaints in this group of patients was over four years.

Significant differences were recognized in the objective manifestations of the patients in Groups I and II.

Normal sinus rhythm was present in all but one of the patients with uncomplicated aortic stenosis. Atrial fibrillation occurred in 47.7% of the patients with coexisting mitral stenosis.

It appeared to us that the clinical manifestations in patients with combined aortic and mitral stenosis much more closely resembled those of the latter disease than of the former.

A loud, rough systolic murmur was heard at the base of the heart in each of the patients comprising Group I. In all but 10.2% this was accompanied by an absent or decreased second aortic sound. When mitral stenosis coexisted (Group II), the intensity of the aortic murmur frequently was decreased, although its rough quality persisted. The second sound was normal in 22% of this group.

The x-ray size of the heart was increased to a degree estimated at 2+ or greater in 65.7% of the patients in Group I and in 82.5% of those in Group II.

The most common electrocardiographic abnormality in Group I was left ventricular hypertrophy, which appeared in 60.6% of the cases. Complete left bundle-branch block was recognized in only 5.6%. In the Group II patients the former abnormality occurred in 15.6%, while the latter did not appear.

TABLE 1.—*Group I—Commissurotomy for "Isolated" Aortic Stenosis*

Anatomical Diagnosis	No. Pts.	Op. Tech.		Deaths		Mort., %	
		TV *	TA †	TV	TA	TV	TA
AS	85	50	35	9	4	18	11.4
AS plus insig. lesions	93	43	50	16	10	37.2	20.0
Totals	178	93	85	25	14	26.9	16.4

* TV indicates the transventricular approach to the aortic valve.
† TA indicates the use of the transaortic approach, using a pouch of entrance.

TABLE 2.—*Group II—Combined Aortic and Mitral Commissurotomy*

Anatomical Diagnosis	No. Pts.	Op. Tech.		Deaths		Mort., %	
		TV	TA	TV	TA	TV	TA
AS, MS	25	21	4	0	0	0	0
AS, MS plus insig. lesions	84	64	20	15	2	23.3	10.0
Totals	109	85	24	15	2	17.6	8.3

TABLE 3.—*Clinical Manifestations*

Manifestation	No. Patients		Per Cent of Total	
	Gr. I	Gr. II	Gr. I	Gr. II
Dyspnea	154	101	86.5	92.6
Fatigue	139	92	78.2	84.1
Angina	86	27	48.2	24.7
Vertigo	55	24	30.9	22.0
Syncope	54	14	30.3	12.8
Paroxysmal dyspnea	38	34	21.3	31.1
Edema	54	67	30.3	61.4
Atrial fibrillation	9	52	5.1	47.7
A wave normal	18	24	10.2	22.0
Heart size over 2+	117	90	65.7	82.5
Electrocardiogram Left ventricular hypertrophy	103	17	60.6	15.6
Left bundle-branch block	10	0	5.6	----

Left-heart catheterization was performed preoperatively in nearly every patient (96.2%) operated on by the transaortic technique (either open or closed). The gradients across the aortic valve ranged from 40 mm. of Hg to 110 mm. of Hg. We have felt generally that definitive surgery for aortic stenosis is not indicated if the gradient is lower than 40 mm. of Hg, except in certain patients with combined mitral and aortic stenosis. In these latter patients, direct measurement of the pressures at surgery, before and after opening the mitral valve, may provide the indication for an aortic attack. While it is felt that "physiological damping" during surgery may lessen the actual level of any measured transvalvular gradient, relief of the mitral obstruction will cause a rise in the transaortic gradient if significant aortic stenosis exists.

Operative Mortality (Tables 1 and 2)

The operative mortality in patients with uncomplicated aortic stenosis was 18% by the transventricular route and 11.4% when the transaortic method was employed. The presence of additional "insignificant" valvular lesions increased the mortality with these techniques, respectively, to 37.2% and 20%. Thus, for all patients in Group I on whom transventricular commissurotomy was performed the risk of death was 26.9%. For those subjected to the transaortic procedure the mortality was 16.4%.

No deaths were encountered with either technique when aortic and mitral stenosis coexisted as "pure" lesions. It is understood that the mitral stenosis was operated on at the same time, using either the left-sided or the right-sided approach. The presence of additional "insignificant" defects (chiefly aortic or mitral insufficiency) increased the transventricular mortality rate to 23.3% and the transaortic to 10%. In Group II, as a whole, the risk of death was 17.6% with the transventricular method and 8.3% with the transaortic.

Of the 11 patients operated on by the open technique, 1 died (ventricular fibrillation during surgery).

The major causes of operative death were correlated with the surgical methods and are listed in Table 4. In each instance death occurred at the time of surgery or during the period of continuous hospitalization following operation.

Clinical Factors Influencing Mortality (Table 5)

In Group I age itself exercised a significant influence on the mortality rate when the transventricular operation was used. The

TABLE 4.—*Major Causes of Death*

Cause	No. Pts.				Per Cent of Total Deaths			
	Gr. I		Gr. II		Gr. I		Gr. II	
	TV	TA	TV	TA	TV	TA	TV	TA
Ventricular fibrillation	16	7	6	2	64	50	40	100
Heart failure	1	1			4	7.1		
Technical errors	5	1	5		20	7.1	33.3	
Cerebral embolism	3	1	2		12	7.1	13.3	
Subacute bacterial endocarditis		1				7.1		
Uremia		1	1			7.1	6.6	
Myocardial infarction		2				14.2		
Transfusion reaction			1				6.6	
Totals	25	14	15	2				

TABLE 5.—*Clinical Factors Influencing Mortality*

Factors	Mortality Rate, per Cent			
	Gr. I		Gr. II	
	TV	TA	TV	TA
Age				
Less than 50 yr.	20.0	17.5	17.5	0.5
More than 50 yr.	61.1	14.2	20.0	25.0
Functional classification				
Classes I and II	12.5	3.5	0	0
Classes III and IV	37.7	22.7	21.1	11.6
Angina pectoris				
Absent	26.3	16.6	15.1	12.5
Present	28.5	16.1	26.3	
Heart size				
2+ or less	27.6	13.7	14.0	7.1
Over 2+	44.4	33.3	25.0	10.0
Congestive failure				
Absent	30.0	16.3	7.7	5.5
Present	30.3	16.5	26.0	16.5

risk was approximately three times greater in patients over 50 years of age. The smaller number of patients in Group II who were beyond 50 years of age prevents a comparative analysis.

A definite correlation between functional classification and survival was demonstrated in the patients of Groups I and II regardless of the operative technique employed.

Although all patients had responded to treatment when congestive failure was present prior to surgery, this complication seemed materially to influence the mortality rate (of both procedures) only in Group II. An increase in heart size adversely influenced mortality in both groups.

The presence of angina pectoris did not alter the mortality rate significantly in either group, regardless of the type of operation selected.

Hospital Complications (Table 6)

In Group I cardiac complications during hospitalization occurred in 19.1% of those operated on by the transventricular method. The conditions encountered included congestive failure, subacute bacterial endocarditis, atrial fibrillation and probable reactivation of rheumatic fever. With the transaortic technique 39.4% developed complications essentially of the same order. In Group II patients no significant statistical difference was observed (between the two types of operation).

TABLE 6.—*Hospital Complications (Cardiac and Embolic)*

Complication	No. of Patients			
	Gr. I		Gr. II	
	TV	TA	TV	TA
Cardiac				
Congestive failure	5	10	7	1
Subacute bacterial endocarditis	2	3	..	1
Atrial fibrillation, converted	5	9	8	1
Atrial fibrillation, permanent	..	2	4	1
Rheumatic fever (?)	1	2	2	..
Embolic				
Cerebral embolus	..	2	1	2
Visceral embolus	..	1	1	..

Follow-Up Review

The postoperative evaluation extends from five months to five years after surgery and includes 231 patients. In this analysis, late deaths, symptomatic improvement, and alterations in objective manifestations are considered separately.

Late Deaths (Table 7).—In Group I there were 41 patients with isolated aortic stenois who had a transventricular commissurotomy and survived. Nine of the series (13%) died after discharge from the hospital. Of those with additional insignificant valve defects, six (14%) died. Thus the late mortality rate following the transventricular operation was 16.1%.

TABLE 7.—*Late Deaths*

Causes	No. of Patients			
	Gr. I		Gr. II	
	TV	TA	TV	TA
Congestive failure	7	2	4	1
Subacute bacterial endocarditis	..	5	..	1
Cerebral embolus	3	..	..	..
Myocardial infarction	1	..	..	..
Unknown	4	6	1	..

Of those who recovered from transaortic commissurotomy, nine patients (25.3% of the series) with uncomplicated aortic stenosis died at a later date. When the valve obstruction was complicated by additional minor lesions, the late death rate was 8%. The total late mortality recorded for this operation was 15.3%.

The comparative figures for patients in Group II indicate a 5.9% incidence of late deaths for the transventricular methods and 8.3% for the transaortic.

TABLE 8.—*Follow-Up Clinical Manifestations in Group I*

	TV					TA				
	Present Preoperatively		Postoperatively *			Present Preoperatively		Postoperatively *		
		Absent	Imp.	S	W		Absent	Imp.	S.	W.
Dyspnea	40	8	18	7	7	51	15	18	9	9
Fatigue	36	3	19	7	7	45	18	15	6	6
Angina	23	8	10	3	2	31	28	..	3	..
Vertigo	19	10	6	3	..	20	16	..	4	..
Syncope	13	11	..	2	..	21	17	1	3	..
Pnd	2	2	..	..	..	13	10	1	1	1
Edema	10	7	2	1	..	16	10	1	3	2
	Preop.	Inc.	Same	Dec.	Prod.	Preop.	Inc.	Same	Dec.	Prod.
Aortic systolic	53	..	33	20	..	58	3	26	29	..
Aortic diastolic	..	..	..	..	30	50	11	38	1	2
↓ or A_2	48	32	16	..	..	53	27	26	..	..
Heart size										
	No change		47			No change		52		
	Decreased		5			Decreased		4		
	Increased		1			Increased		2		

* S indicates "same"; W, "worse."

Congestive failure was the most common cause of death after discharge from the hospital. This developed in 14 patients, 11 of whom were operated on by the transventricular technique. In some instances it appeared to be related to the inadvertent creation of aortic insufficiency or its aggravation by the surgical procedure.

Subacute bacterial endocarditis was diagnosed in six patients at some point from the time of hospital discharge through the duration of this follow-up study. This complication occurred only after transaortic commissurotomy. Accordingly, the likelihood of subacute bacterial endocarditis following recovery from this procedure was 6.4%.

The average time of death following transventricular commissurotomy was over 20 months, as compared with 4 months following application of the transaortic technique. This probably is a reflection of the relative lengths of the follow-up of the two series.

Symptomatology (Tables 8 and 9)

A gross analysis of the follow-up data does not disclose any significant differences between the two major anatomic groups or in the groups operated by the two different techniques.

Approximately 70% of the presently living patients have been definitely improved as a result of surgery insofar as subjective

TABLE 9.—*Follow-Up Clinical Manifestations in Group II*

	TV					TA				
	Present Preoperatively		Postoperatively			Present Preoperatively		Postoperatively		
		Absent	Imp.	S.	W.		Absent	Imp.	S.	W.
Dyspnea	63	8	38	10	7	20	3	12	3	2
Fatigue	60	6	33	14	7	19	3	11	3	2
Angina	13	7	4	..	2	6	4	..	1	1
Vertigo	14	10	4	..	..	7	5	2	..	..
Syncope	7	5	..	2	..	3	3	..	..	..
Pnd	18	15	..	3	..	4	4	..	..	..
Edema	42	18	10	6	8	10	4	2	2	2
	Preop.	Inc.	Same	Dec.	Prod.	Preop.	Inc.	Same	Dec.	Prod.
Aortic syst. M.	65	..	35	30	..	20	..	20	..	..
Aortic diast. M.	..	..	..	..	35	16	2	14	..	4
↓ or A_2	58	28	30	..	..	20	..	20	..	..
Heart size										
	No change		54			No change		20		
	Decreased		8			Decreased		..		
	Increased		3			Increased		..		

complaints and functional capacity are concerned. Fifteen per cent show no improvement, whereas the remaining fifteen per cent consider themselves to be worse now than before operation. In part this latter group represents the naturally-to-be-expected retrogression of those in whom an inadequate restitution of valve function has been accomplished. In others, the creation of an additional element of valvular incompetence may be responsible.

The most dramatic improvement was observed in the symptom triad of angina, vertigo, and syncope. Approximately 80% of those who experienced these preoperatively either no longer had these complaints or noted marked improvement.

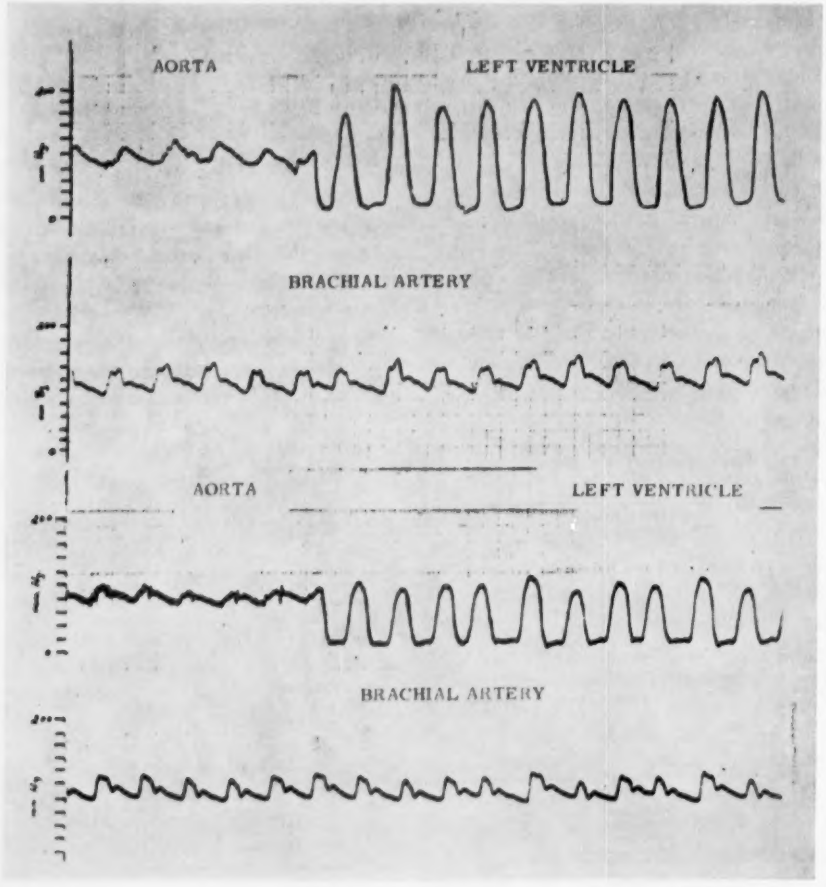
Fatigue, exertional dyspnea, and edema likewise disappeared or were ameliorated considerably in 65%.

Objective Manifestations (Tables 8 and 9)

The objective changes noted after operation were less dramatic and bore no direct statistical relation to the subjective improvement noted by the patients.

The aortic systolic murmur was unchanged in over 58% of the patients regardless of which technique was used. The

Fig. 16A.—Preoperative (above) and postoperative (below) findings during left heart catheterization of a patient who underwent digitally guided aortic commissurotomy by the closed transarterial method. Note practically complete abolition of transaortic (systolic) gradient (80 mm. of Hg to 5 mm. of Hg).



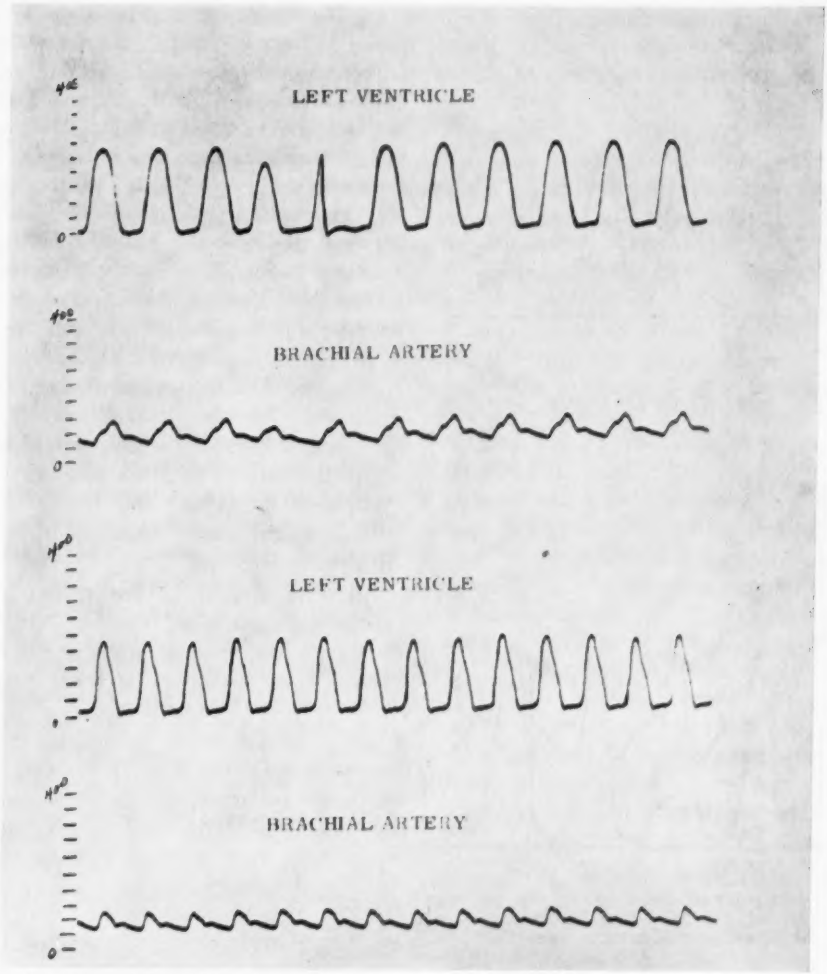


Fig. 16B.—Unsatisfactory result obtained in another patient who survived transaortic commissurotomy (closed).

aortic second sound remained decreased in 52% of those patients in whom it was diminished or absent prior to operation. However, it became more prominent in the remainder.

Significantly, however, the murmur of aortic insufficiency was heard in 69 patients (53%) who did not have this murmur previously. In seven of these patients this murmur represented dynamic aortic insufficiency, an incidence of 5%.

A marked decrease in the heart size was noted in 17 patients (9%). Six patients (3%) showed a definite increase in cardiac size. Significant alteration in the electrocardiographic pattern was not noted.

The pressure gradient fell postoperatively in 16 of the 18 patients who were catheterized both pre- and postoperatively by the left-heart technique of Björk [37] and Fisher [38] (Figs. 16A, 16B, and 16C). In two, no change was observed. The significance of the positive results must involve altered physiological elements, including cardiac output. The correlation of these findings as a reflection of the effectiveness of surgery

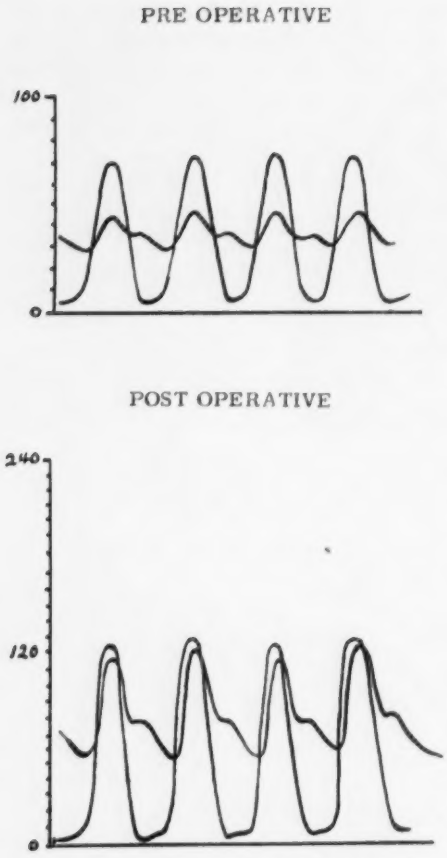


Fig. 16C.—Excellent result obtained in patient whose aortic stenosis was relieved by the open technique, using a heart-lung bypass and retrograde perfusion of the coronary sinus (45 mm. of Hg gradient reduced to 8 mm. of Hg).

is the subject of considerable current investigation.

Results of Open Aortic Commissurotomy

It obviously is futile to attempt at this time any profound analysis of the results of this very new procedure in which our earliest case is less than three months postoperative. However, the foregoing review of the two existing older surgical procedures strongly suggests the need for a more effective alternative which would seem to be offered by the open method. Hence, we shall summarize our present experience.

Of the 11 patients operated on by the open technique, using the Friedländ-Gemeinhardt bypass apparatus and retrograde perfusion of the coronary sinus, all but one have survived to date. Three were cases of congenital valvular stenosis. The remaining eight had isolated calcific, probably rheumatic, aortic stenosis. Thus, all belonged to Group I. Three patients had associated "insignificant" aortic insufficiency. One of them, a congenital case, presented an increased "pulse pressure."

Their ages varied from 14 to 55 years. Nine presented symptoms of myocardial insufficiency (dyspnea, failure), and six showed evidences of coronary insufficiency (anginal pain). Four had suffered from vertigo and syncope.

Body weights varied from 113 to 174 lb. All patients were males.

All were studied by left or combined cardiac catheterization preoperatively, and the transaortic gradients during systole were estimated by planimetry at levels varying from 40 to 150 mm. of Hg.

The respective periods of cardiopulmonary bypass varied from 5 to 23 minutes. The maximum perfusion rate in these patients varied from 2000 to 3600 cc. per minute. These were based upon the venous return and varied from 60-80 cc. per kilogram per minute. This rate was reduced sharply at the time of reestablishment of cardiac function, usually to 1000 cc. per minute.

At surgery, but one commissure was found partially open in six patients; two commissures were partially open in two, and the three commissures were reduced equally in the other three patients. In four patients, with unicommissural passages, only one of the remaining commissures was separated because the anatomicopathological picture suggested that regurgitation might follow division of the other.

In two patients, free fragments of calcium were dislodged by the instrumentation. In each the particles were picked up and removed from the aorta with thumb forceps. However, one of these patients did suffer

from a transient hemiphlegia which suggested that an additional calcific fragment might have been overlooked at the time of surgery (perhaps falling back into the ventricle), or that it may have broken off after the cardiac function was restored. In an additional patient, craggy calcific excrescences were rongeured away. In 4 of the 12 patients, one of the commissures was left unopened at surgery because of extreme calcification and distortion and the fear of causing aortic regurgitation should an inaccurate separation be produced.

One patient developed ventricular fibrillation during the period of bypass, and this proved to be intractable. It is believed that an excessive amount of perfusion of the coronary sinus may have been responsible (over 400 cc. per minute) for this complication. It has been our policy to adjust the rate of coronary perfusion to that amount which produces a slow but constant exudation of dark blood from the coronary ostia. Usually this is accomplished at a perfusion rate of 75 to 200 cc. per minute.

One other patient developed ventricular fibrillation after closure of the aortic incision and restoration of cardiac function. At this time, inspection of the anterior descending branch of the left coronary artery revealed the presence of air bubbles within its lumen. Maintenance of a low rate of aortic perfusion (1000 cc. per minute) and vigorous cardiac massage with intermittent clamping of the ascending aorta as recommended by Geoghegan and Lam[39] resulted in their disappearance. Subsequent application of electric countershock eventuated in restoration of a normal sinus rhythm and survival.

Since this experience with air embolism, at the suggestion of one of our associates, Dr. Houck E. Bolton,[40] we routinely have flooded the entire thoracic cavity and the opened portions of the cardiovascular structures with gaseous carbon dioxide during all of our bypass procedures. We feel that a certain incidence of gaseous embolization must be inherent in such operations. Hence, it is advisable to displace the air content of these structures with the heavier carbon dioxide, which is relatively well tolerated (quickly absorbed) within the arterial passages.

A very special and meticulous technique of mechanical hemostasis has been practiced, and the heparin required during the bypass has been neutralized with one and one-half this amount of protamine sulfate. With these measures postoperative bleeding has not been a problem.

Postoperatively, all surviving patients have done well clinically. It would seem that the presenting symptoms have been overcome in each instance. However, only time will permit a proper evaluation of this aspect of their results.

In no instance has there been any suggestion of creation of valvular insufficiency. On the contrary, minimal degrees of preexisting aortic insufficiency seem to have been abolished in two patients. The widened pulse pressure referred to previously was reduced to within normal limits.

The aortic systolic murmur has been reduced in intensity in all but four patients. In three it now is barely perceptible to ordinary auscultation.

Postoperative left-heart catheterization has been carried out in only three patients. In each, a very gratifying reduction in the level of the aortic gradient has been apparent (Fig. 16C).

Comment

The evaluation of the surgical treatment of aortic stenosis requires an examination of the risks involved and the ability of the respective procedures to alter the physiologic and clinical expressions of the disease. The current appraisal is set against the background of two established techniques for the relief of aortic stenosis (and one very new one) and is tempered by the fact that in many instances either one was performed in association with a simultaneous mitral commissurotomy. The inclusion of material with such a broad base, however, permits many areas of comparison which were denied in previous studies.[41,42]

A comparison of operative mortality reveals that the transventricular method offers approximately twice the risk which is associated with the transaortic technique except when aortic and mitral stenosis coexist as the only valve defects. The latter category of patients is indeed unique, since all those with "pure" aortic and mitral stenosis who were operated on survived. An explanation is suggested from this analysis which indicates that the clinical manifestations of aortic stenosis are more severe when the lesion exists alone or in combination with other insignificant valve defects than when associated with major mitral stenosis. It is a logical working hypothesis that mitral stenosis decreases the blood flow per unit of time into the left ventricle, thus modifying the relative magnitude of the aortic obstruction and sparing this chamber from the full physiologic impact of that anatomic lesion. Since the functional integrity of the left ventricle respresents a most critical item in the response of patients with acquired valve lesions to surgical treatment, this protective effect may account for the success which was independent of the particular surgical technique employed. An additional factor was the lower incidence of such factors as extreme calcification of the aortic valve, which is less often found in combined disease. Smaller degrees of pathological change, even though associated with an equal degree of commissural fusion (and, hence, of physiological obstruction), render it more readily possible for a true and accurate aortic commissurotomy to be accomplished by any technique.

A pertinent question arises as to the increase in mortality rate when "insignificant" lesions complicate aortic stenosis either alone or in combination with mitral stenosis. The explanation must rest with our inability to judge critically the burden imposed by defects which appear innocuous according to the usual criteria. For example, it is reasonable to suspect that the additional abnormal physiology accruing from complicating aortic insufficiency compromises the risk of surgery even though the lesion does not produce a wide pulse pressure or a grossly dilated left ventricle. This realization is in sharp contrast to earlier reports, suggesting that the presence of adynamic coexisting lesions did not influence the operative mortality materially.

Although the present review indicates the superiority of the transaortic approach from the standpoint of immediate mortality, this view must be tempered by the fact that a smaller number of patients, particularly those with combined lesions, have been subjected to that operation. Furthermore, while more extensive valvular mobilization may be accomplished in this manner, it is feared that serious degrees of insufficiency likewise may be created more easily. The late mortality in several of our patients seemed to be due to such a lesion.

Theoretically transaortic commissurotomy offers a distinct advantage in not entailing direct trauma to the hypertrophied and often irritable left ventricle. However, the hope that this would be reflected in abolition of ventricular fibrillation during surgery was not realized. It is apparent that the risk of ventricular fibrillation, although reduced by the transaortic approach, must be accepted as an unpredictable hazard in surgery for aortic stenosis.

The ability to palpate the aortic valve during the performance of transaortic commissurotomy appears to offer a better opportunity to avoid areas of calcific encrustation and hence, the precipitation of embolic issue. The technique, however, does not offer absolute protection against that complication.

The death of patients following recovery from aortic commissurotomy must be accepted as an indictment of treatment. These failures arise as a result either of an inadequate operation or of succeeding complication.

Recently an attempt has been made to define the reasons for an ineffective operation by correlating the valve morphology, the enlargement of the aortic orifice obtained by surgery, and the clinical results.[43] This analysis suggests that 20% of the patients

with severe manifestations of aortic stenosis possess such heavily calcified, fixed valves that there is but a limited possibility of increasing the size of the orifice materially by any closed method except at the price of creating incompetence. When to these are added the number of patients who suffer an actual complication of surgery the risk of failure is extended.

Therefore, if late deaths serve as an indication of insurmountable morphologic changes or severe complications, there is an insignificant difference in the results obtained, respectively by the transventricular and transaortic techniques. Further support for that contention is derived from the actual incidence of dynamic aortic regurgitation produced at surgery which is nearly identical for both types of closed operation. It is felt that the advent of the open technique for the performance of aortic commissurotomy significantly increases our ability to mobilize the most extensively pathologic valves with less risk of creating insufficiency.

An unusual incidence of the occurrence of subacute bacterial endocarditis is observed following the transaortic commissurotomy. Since this complication in four instances developed but a short period after surgery, the cause must be suspected most logically to rise from a fault in sterile technique or in inadequate antibiotic protection. The transaortic method requires the use of the ungloved finger to provide the exquisite sensitivity of the bare digit for critical examination of the valve. Although a meticulous preoperative preparation of the hand has been practiced, the suspicion remains that the offending organism may have been introduced during surgery in these patients. However, in two instances the infection developed more than one year after operation, which would seem to support a view that the extreme trauma to which the aortic valve is subjected during normal function may favor bacterial lodgment and growth, especially after the insult of surgical incision.

The percentage of patients improved and the degree of subjective benefit obtained are not extended significantly by the transaortic operation over those achieved by the transventricular one. This is also true when the objective manifestations are reviewed.

Analysis of the data supplied by left heart catheterization prior to and following transaortic commissurotomy revealed numerous examples of persistent pathologic pressure gradients at the conclusion of surgery. Even though clinical improvement has been observed in patients with small alterations in gradient, it remains a distressing realization that the pattern of surgical achievement is not consistent enough to include routinely a great obliteration of the basic dynamic effect of aortic valve obstruction.

This critical review is not a denial of surgery as a therapeutic agent, because the striking clinical improvement enjoyed by the vast majority of surviving patients extends into such basic complaints as angina, syncope, and dyspnea. However, it does emphasize the wisdom of current interest in the open technique for aortic commissurotomy. Theoretically, if the heart-lung bypass and coronary perfusion techniques do not aggravate the immediate mortality, it is logical to envision a more perfect anatomic correction of the valve without serious complication regardless of the morphologic hindrance. This latter presumption appears to be justified fully by even the present limited experience with this method. In the interim the techniques now generally available offer a very reasonable means of altering the basic devolutionary trends of aortic stenosis.

Summary and Conclusions

The immediate mortality and the clinical and physiologic responses of 287 patients operated on for aortic stenosis by the transventricular and transaortic techniques are reviewed. A report of our early experience with the open technique for aortic commissurotomy is included.

Although the closed transaortic technique is associated with a much lower initial operative mortality, the number of late deaths, the average time of their occurrence, and the postoperative clinical response all contribute to an approximate equalization of the value of the two closed procedures.

Approximately 70% of the patients have been improved following surgery, the most dramatic benefits occurring in the symptom triad of angina, vertigo, and syncope.

Objective changes after operation are less striking and bear no direct relation to the degree of reported subjective improvement.

Both closed operative methods are capable of reducing the pressure gradient measured across the aortic valve, but this is not an entirely consistent effect. Their most gratifying and reliable accomplishments with respect to operative survival, clinical improvement, and abolition of the differential between aortic and left ventricular pressures have been noted in patients with combined aortic and mitral stenosis. Presumably this is related chiefly to the lower degree of aortic pathological change which these patients are prone to present, even in the presence of severe obstruction.

It is concluded that the closed techniques are adequate and safest in patients with acquired aortic stenosis without radiographic evidence of calcification and in those with combined aortic and mitral stenosis.

It is felt that the open technique employing a heart-lung bypass and retrograde perfusion of the coronary sinus should be used in all operative cases of congenital aortic stenosis and in most patients with extensive calcification of the aortic valve. The exquisite accuracy of commissural division which it permits would seem routinely to provide maximal relief of the obstruction without any decrease in the valve competency. Nevertheless, in patients with extreme valvular pathology, it is obvious that the possibility of reconstitution of valve function may be sharply restricted.

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Adrenocortical Function in Long-Term Treatment with Corticoids

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It has been definitely established that the administration of cortisone results in suppression of adrenocortical function and atrophy of the adrenal cortex.[1] These effects are believed to be due to suppression of secretion of corticotropin. The purposes of the current study were threefold: first, to determine the degree of adrenocortical responsiveness, if any, to the stimulus of exogenous corticotropin (ACTH) in patients receiving continuous therapy with cortisone, hydrocortisone, and/or prednisone. (These three corticoids will be subsequently referred to simply as cortisone.) The second purpose was to determine the influence, if any, of the daily dose of cortisone and/or the duration of therapy on the degree of adrenocortical response to corticotropin. The third purpose was to observe the change, if any, in responsiveness to corticotropin in persons who had been so tested twice before, and under identical conditions, while being maintained on long-term and continuous treatment with cortisone.[2,3]

Data on Twenty-Two Male Patients

			1953			1954			1956		
Patient	Age	Diagnosis	Therapy, Mo.	Dose, Mg.*	Response, Day	Therapy, Mo.	Dose, Mg.*	Response, Day	Therapy, Mo.	Dose, Mg.*	Response, Day
1	51	Rheum. arth.	17	75.0 C	5	30	100.0 C	5	49	10.0 P	5
2	35	Rheum. arth.	20	87.5 C	3	33	75.0 C	3	53	75.5 C	4
3	40	Rheum. arth.	24	100.0 C	2	36	100.0 C	3	59	17.5 P	4
4	39	Rheum. arth.	26	75.0 C	3	36	75.0 C	3	58	62.5 C	1
5	30	Rheum. arth.	25	50.0 C	2	37	50.0 C	3	56	37.5 C	2
6	46	Rheum. arth.	26	75.0 C	3	38	75.0 C	3	60	15.0 P	3
7	31	Rheum. arth.	26	75.0 C	4	39	75.0 C	1	61	75.0 C	5
8	37	Rheum. arth.	26	62.5 C	4	39	62.5 C	4	61	40.0 H	3
9	51	Rheum. arth.	29	100.0 C	1	41	75.0 C	4	64	87.5 C	3
10	34	Rheum. arth.	29	50.0 C	3	42	37.5 C	4	58	37.5 C	2
11	62	Rheum. arth.	33	87.5 C	4	46	100.0 C	3	67	12.5 P	5
12	43	Rheum. arth.	34	75.0 C	3	48	75.0 C	>5	65	75.0 C	5
13	57	Rheum. arth.	36	50.0 C	>5	49	75.0 C	4	69	12.5 P	5
14	67	Rheum. arth.	38	50.0 C	3	50	37.5 C	3	70	37.5 C	1
15	35	Rheum. arth.	13	75.0 C	2	...	...	...	39	50.0 C	1
16	45	Rheum. arth.	...	...	...	35	75.0 C	3	54	75.0 C	3
17	44	Eczema	...	...	...	41	62.5 C	3	62	37.5 C	3
18	45	Rheum. arth.	...	...	...	...	...	...	32	15.0 P	3
19	51	Rheum. arth.	...	...	...	37	100.0 C	5	57	12.5 P	4
20	27	L. E.	...	...	...	...	...	...	41	62.5 C	4
21	34	Rheum. arth.	...	...	...	...	...	...	29	12.5 P	2
22	29	Rheum. arth.	...	...	...	...	...	...	46	75.0 C	5

* C indicates cortisone; P, prednisone; H, hydrocortisone.

The subjects of this study were 22 male patients, of whom 20 had rheumatoid arthritis, 1 had lupus erythematosus, and 1 chronic eczema (Table). Their ages ranged from 27 to 67, with the average age 43. Their daily doses of cortisone were from 37.5 to 87.5 mg., with an average daily dose of 62.5 mg.; hydrocortisone and prednisone were used in corresponding antirheumatic doses. The duration of continuous therapy

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From the Medical Service, Veterans' Administration Hospital; University of California and Stanford University Schools of Medicine.

	DAYS OF R						DAY OF RSPNSE
	0	1	2	3	4	5	
Eosinophils fasting		160	204	198	57	12	3
3:15 p.m.		114	87	45	21	0	
17-ketosteroids	8.2	7.2	11.9	21.9	30.0	33.7	3
E Corticoids	0.0	0.2	0.65	3.4	5.9	5.4	2

Fig. 1.—Adrenocortical response to corticotropin. The initial eosinophil count was 160, and it was not until the third successive day of administration of corticotropin that the required drop in eosinophils occurred. The required increase in 17-ketosteroids also occurred on the third successive day of corticotropin. The required increase in urinary free corticoids occurred on the second successive test day. Since two of the three criteria were not met until the third day, this patient's adrenocortical response was regarded as demonstrated satisfactorily on the third successive day of corticotropin administration and was so recorded.

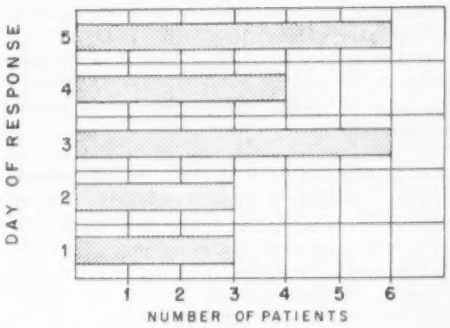

Fig. 2.—Day of adrenocortical response in 22 patients tested in 1956.

in these 22 patients averaged 55 months, with the range from 29 to 70 months. None had had intermittent therapeutic courses of corticotropin.

Method of Study

Each patient was hospitalized for six days, during which time he received his usual daily dose of cortisone. The first 24-hour period served as a control day, Day 0. Five test days followed, Day 1 through Day 5. On Days 1 and 2, each patient received 25 units of corticotropin by intravenous infusion over a three-hour period. On Days 3, 4, and 5, each received 25 units of corticotropin intravenously over a 16-hour period. The daily urinary output, including that of control Day 0, was assayed for 17-ketosteroids by the method of Klendshoj,[4] with modifications by Zenker and Biskin, and for free corticoids by the method of Porter and Silber.[5] Total eosinophil counts by Pilot's method[6] were obtained at 9 a. m. (a fasting sample) and 3:15 p. m. daily on Days 1 through 5.

The corticotropin infusion time of three hours was chosen for the first two test days in order to provide minimal stimulus to the adrenal cortex. Using similar criteria of cortical response to corticotropin, it has been shown that untreated subjects with presumably normal adrenals consistently demonstrate adequate cortical response following a single three-hour infusion of 25 units of corticotropin.[7] The same criteria of cortical responsiveness were used for the subjects of this study. Adrenocortical responsiveness was believed to be demonstrated on that day of administration of

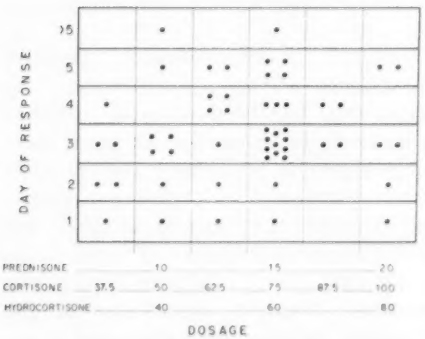

Fig. 3.—Correlation of dosage of steroids and day of adrenocortical response (22 patients, 54 tests).

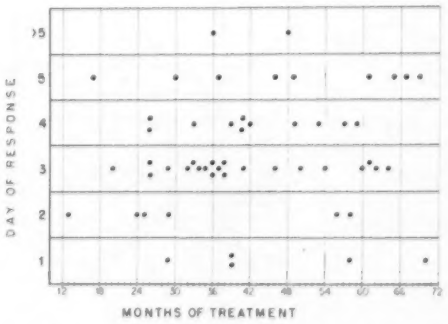

Fig. 4.—Correlation of duration of treatment with steroids and day of adrenocortical response (22 patients, 54 tests).

corticotropin when any two of the following three criteria were fulfilled:

1. A drop in eosinophils of 50% or more compared to the fasting count on Day 1, provided the same or greater decrease was found on the following day.

2. An increase in urinary 17-ketosteroids of 50% or more compared with the control specimen.

3. An increase in urinary free corticoids of 50% or more as compared with the control specimen, with a minimum rise of 0.5 mg.

The data obtained from one of these patients (Fig. 1) demonstrates how the day of adequate adrenal response was arbitrarily determined.

Results

The day of adrenocortical response to corticotropin in the 22 patients is shown in Figure 2. Only three patients showed an adequate normal response on Day 1.

In order to determine whether the daily dose of cortisone correlated with the day of response, the results of 54 tests on these 22 patients from the present and two previous studies, are tabulated in Figure 3. It is apparent that adrenal responsiveness to corticotropin is independent of the dose of steroids (at least in the doses used).

The results of the same 54 tests are plotted in Figure 4, to demonstrate the relationship between the months of treatment with cortisone and the day of adrenocortical response. Obviously, there is a complete lack of correlation between the duration of therapy and day of response.

Of these 22 patients, 14 were tested identically in 1953,[2] 1954,[3] and 1956, thereby permitting serial demonstration of adrenocortical responsiveness during continuous therapy with cortisone as shown in Figure 5. This graph demonstrates the lack of any typical pattern for the group and the variation in adrenocortical response to corticotropin from year to year in the individual patient; this apparent inconsistency was independent of the daily dose of cortisone or the duration of treatment. It is of some interest that, despite continuous therapy with cortisone, there was no progressive decrease in adrenocortical responsiveness to corticotropin.

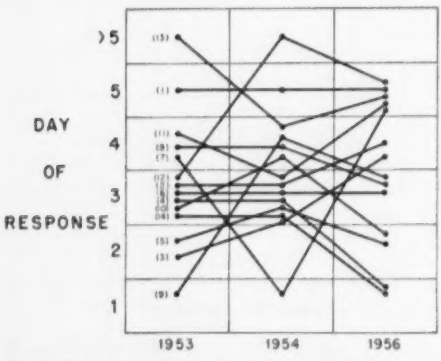

Fig. 5.—Adrenocortical response in three successive tests on 14 patients receiving continuous therapy with steroids.

Comment

Most of these patients required repeated daily stimulation with corticotropin before adrenocortical response could be demonstrated. This is further evidence that a dormant state of the adrenal cortex is induced by cortisone, even by so-called maintenance doses. This reemphasizes the need for constant vigilance in situations of stress, which may necessitate larger doses of cortisone to compensate for the inability of the pituitary-adrenal mechanism to respond spontaneously. Patients receiving cortisone therapy may require additional cortisone during illness or after injury, as do patients with Addison's disease. Moreover, the delay in adrenal responsiveness to corticotropin during treatment with cortisone adds further support to the clinical observation that sudden discontinuation of cortisone is hazardous.

Since all of these patients ultimately demonstrated adrenal responsiveness, even though they had been receiving cortisone continuously for as long as six years, there would appear to be no need for the intermittent withdrawal of cortisone to protect against irreversible adrenal atrophy; nor should intermittent courses of corticotropin be necessary during long-term therapy with cortisone. It may be argued that the frequent administration of corticotropin during therapy with cortisone would allow for better adrenocortical response during periods

of stress; however, extremely large doses of corticotropin would presumably be necessary. According to Wolfson and Young, weekly doses of 160 to 400 units of corticotropin, given intramuscularly, are required to maintain normal adrenocortical responsiveness during concomitant treatments with cortisone.[8] These doses of corticotropin are within the therapeutic range and if used alone would eliminate the need for maintenance doses of cortisone.

Summary

Each of 22 patients who had been given continuous maintenance doses of cortisone for an average duration of 55 months showed adrenocortical response to exogenous corticotropin; however, responsiveness was delayed in 19 of these patients.

There was no correlation between the daily doses of cortisone or the duration of treatment and the adrenocortical response to corticotropin.

In 14 patients tested serially and identically over a period of years, no consistent trend in adrenocortical responsiveness to corticotropin could be demonstrated.

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Carbohydrate Metabolism in Brain Disease

X. Lack of Effect of Chlorpromazine and Reserpine on Abnormal Carbohydrate Metabolism in Chronic Schizophrenia

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Earlier work done in this laboratory has shown that patients with schizophrenic, manic-depressive, and involutional psychoses have a disorder of carbohydrate metabolism.[1] The fact that chlorpromazine and reserpine improve the behavior of patients with these syndromes is well known. However, it is difficult to establish the efficacy of any medication in affective psychoses, since these disorders are usually self-limited. It was therefore decided to study the carbohydrate metabolism of chronically schizophrenic patients who improved while receiving these medications.

Material and Methods

Five women, ranging in age from 26 to 49 years, were studied. All were well nourished and free of intercurrent disease. Observations were made on changes that took place in various blood constituents after the administration of 100 gm. of glucose by mouth. The methods used were as previously described.[1]

Observations

CASE 1.—Woman, age 49 years. The patient had been hospitalized continuously for the last 10 years and intermittently during the preceding 7 years. In other respects her history was not remarkable. She had been receiving chlorpromazine, 25 mg. by mouth four times daily, for seven months at the time of study, and her clinical status had improved on this regimen. Measurements made after the patient was given 100 gm. of glucose by mouth showed abnormal rises in blood lactic, pyruvic, and citric acid levels (Fig. 1).

CASE 2.—Woman, age 26 years. The patient had been hospitalized continuously for the previous three years. In other respects her history was not remarkable. She had received reserpine in various doses for two months until six months before the present study. After that time the patient was given chlorpromazine, 50 mg. by mouth three times a day, for six months, i. e., until the time of study; her clinical status had improved. Measurements made after she was given 100 gm. of glucose by mouth showed abnormal rises in blood glucose and in blood lactic, pyruvic, citric, and α-ketoglutaric acid levels (Fig. 2).

CASE 3.—Woman, age 31 years. The patient had been hospitalized continuously for the last three years, although she had shown intermittent psychotic behavior for five years before admission. She had hypertension of unknown origin, but in other respects her history was not remarkable. The patient had received chlorpromazine in doses of between 150 and 225 mg. by mouth daily for 2 months, ending 18 months before the present study. After a brief hiatus she was given reserpine, in varying doses; at the time of study she was receiving 1 mg. three times a day by mouth. Her clinical status had improved. Measurements made after the administration of 100 gm. of glucose by mouth showed excessive rises in blood lactic, pyruvic, and α-ketoglutaric acid levels (Fig. 3).

CASE 4.—Woman, age 36 years. The patient had been hospitalized continuously for the previous two years and once, two and one-half years before her present admission, for eight months. She had undergone herniorrhaphy at the age of 6, appendectomy at 17, oophorectomy at 18, and hysterectomy at 22; she had had asthma in childhood and undulant fever at 15. The patient had been taking reserpine in various doses for 11 months; at the time of study the dose was 1 mg. by mouth twice daily. Her clinical status had improved. Measurements made after the administration of 100 gm. of glucose by mouth showed

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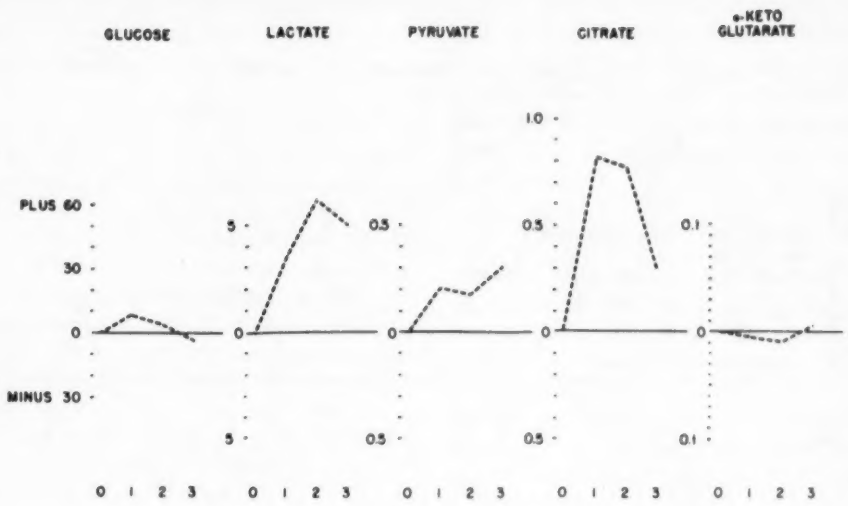

Fig. 1.—Findings in Case 1.

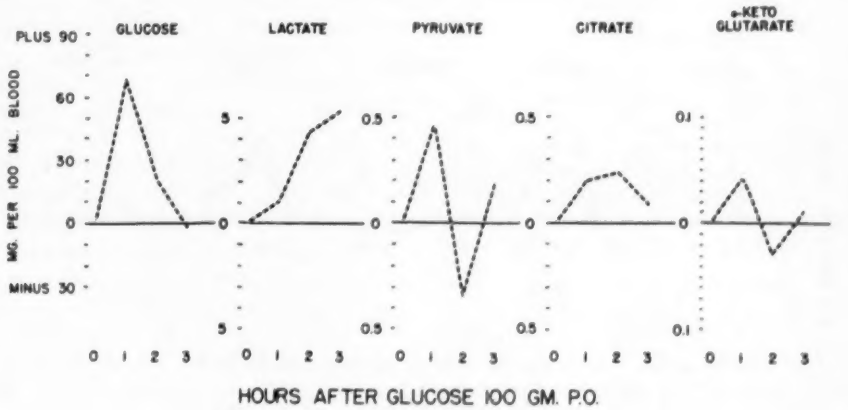

Fig. 2.—Findings in Case 2.

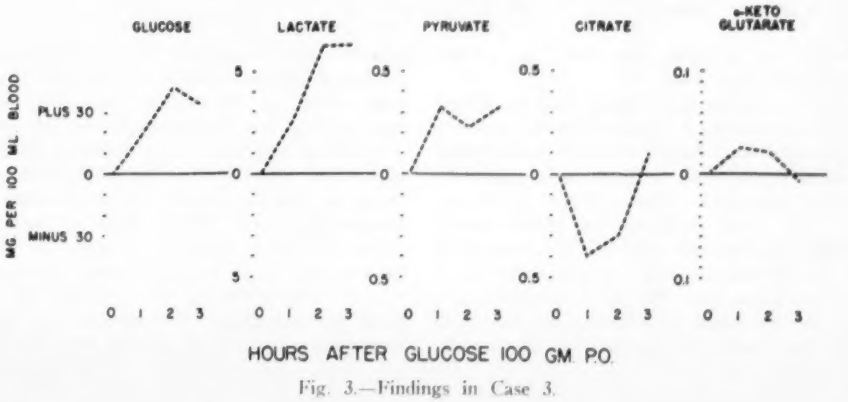

Fig. 3.—Findings in Case 3.

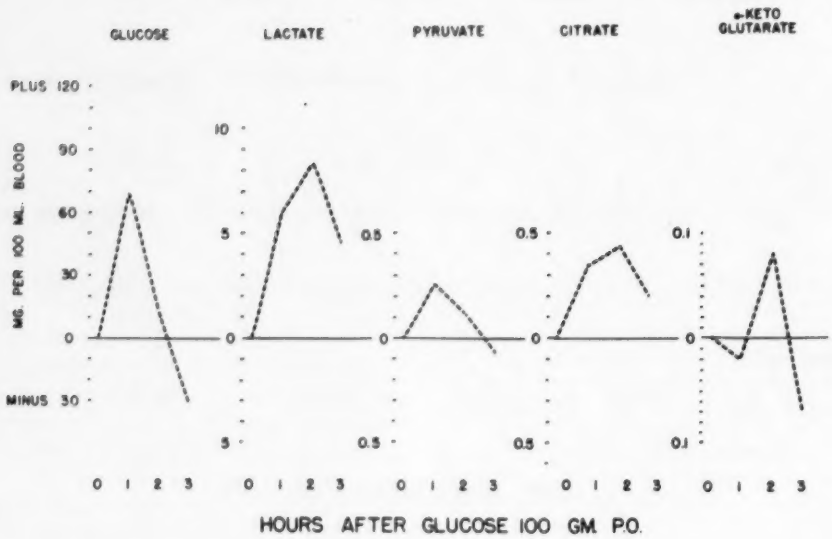

Fig. 4.—Findings in Case 4.

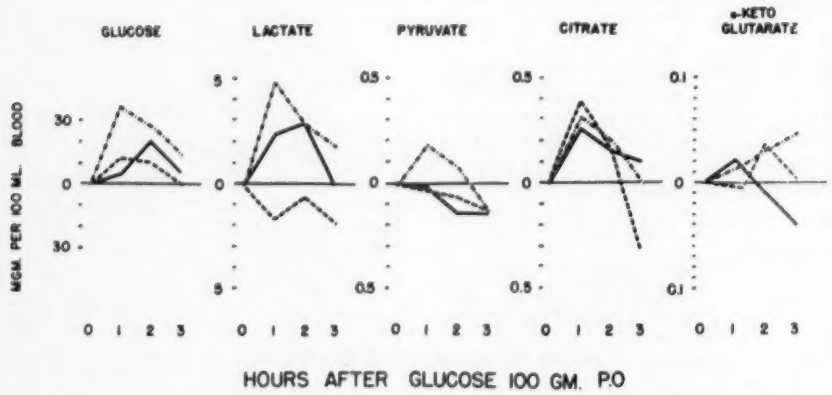

Fig. 5.—Findings in Case 5. The solid lines indicate data obtained before treatment. The broken lines indicate data obtained after five months of treatment. The dash-dot lines indicate data obtained after 19 months of treatment.

excessive rises in blood lactic, citric, and α-ketoglutaric acid levels (Fig. 4).

Case 5.—Woman, age 26 years. The patient had been hospitalized since November, 1954, except for a five-month visit home. She had had arthritis some years previously, but her history was otherwise not remarkable. Her first test, which was made before any medication was given, showed excessive rises in lactic and citric acid levels after the administration of 100 gm. of glucose by mouth. The patient was given 180 mg. of chlorpromazine daily for six weeks in February and March of 1955. Two weeks later she was started on reserpine in varying doses, and her clinical status improved. Repetition of the test in July, 1955, after three months of this regimen, showed excessive rises in blood citric and α-ketoglutaric acid levels. The patient was able to go home on visit, although she was far from her prepsychotic self. However, after five months she had to reenter the hospital (in April, 1956). While at home the patient had taken 1 mg. of reserpine by mouth twice a day. After her readmission, chlorpromazine, in doses of 150 mg. by mouth per day, was added to her regimen. Repetition of the test 10 weeks after readmission showed excessive rises

in blood lactic, citric, and α-ketoglutaric acid levels (Fig. 5).

Comment

The administration of chlorpromazine or reserpine in the cases described above caused improvement in behavior according to clinical criteria. Nevertheless, all the patients still showed the abnormalities of intermediary carbohydrate metabolism that are found in untreated schizophrenic patients.[1] It is evident, therefore, that the drugs did not affect the fundamental disease process. The patients were given psychotherapy in varying degrees of intensity while receiving the medications; nevertheless, it was not possible to discharge them.

Few data on the effects of tranquilizing agents on the abnormal physiology of mental disease have been published. Azima and Richman[2] described a rise of the plasma copper level in patients given chlorpromazine. This, however, represents no improvement, since many patients with mental diseases have elevated copper levels to begin with.[3] Shankel and Whittier,[4] on the other hand, reported that the abnormal cardiovascular responses to epinephrine and methacholine (Mecholyl) that occur in schizophrenia became normal when the patients were given reserpine; however, they observed this phenomenon even in patients who showed no clinical improvement.

The observations presented here, together with those reported by others, help to define the clinical action of chlorpromazine and reserpine. The drugs improve behavior and make it possible for the patients to have a more nearly normal hospital environment than has heretofore been feasible; however, their clinical effects cannot be correlated with improved physiologic status. Their action, therefore, is that of modifying symptoms[5]; they do not affect the fundamental disease process.

Summary and Conclusions

Studies of carbohydrate intermediary metabolism in five patients with chronic schizophrenia were made after each subject had taken chlorpromazine or reserpine, or both, for between 7 and 19 months. All showed clinical improvement while receiving the drugs, but in each case the carbohydrate metabolism remained markedly abnormal.

These findings suggest that chlorpromazine and reserpine improve behavior but do not modify the underlying disease process.

McLean Hospital.

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Atrial Fibrillation Following Mitral Valvulotomy

A Study of Its Clinical Characteristics and Predisposing Factors

RANDAL HEINZ, M.D., and HERBERT HULTGREN, M.D., San Francisco

The commonest postoperative complication following mitral valve surgery in patients with a normal sinus rhythm is the occurrence of atrial fibrillation. This may appear in 24% to 38% of all such patients. Although in a majority of cases sinus rhythm may be reestablished either spontaneously or with the aid of quinidine, a small percentage of patients will continue to fibrillate permanently following surgery. Because of the increasing application of surgery to acquired heart disease, this iatrogenic arrhythmia deserves systematic study. In addition, an examination of its characteristics may add to our knowledge of the genesis of this common disorder of cardiac rhythm. For these reasons, the records of 144 patients subjected to mitral valvulotomy were reviewed in order to examine the following features of postoperative atrial fibrillation:

1. Clinical characteristics.
2. Predisposing factors.
3. Effect of digitalis and quinidine.

Material

During the period from Nov. 1, 1950 to March 1, 1956, a total of 164 mitral valvulotomies were performed at the Stanford University Hospitals. There were 14 fatalities during surgery or in the immediate postoperative period, an operative mortality of 8.5%. (One fatality was the result of a second valvulotomy for restenosis of the mitral valve.) None of these fatalities were included in the study. Six records were unavailable for examination, so that adequate data were obtained from 144 patients. In most instances the information was obtained from the clinical records although about half of the patients had been personally observed by one of the authors.

The observations were made only during the initial hospital entry for surgery. Information regarding the subsequent course of these patients was incomplete.

The sex ratio and age incidence of the 144 patients are summarized in the Table and compared with data of other reported series of patients with mitral stenosis. The groups are comparable. The functional classification of the patients in this series was essentially similar to that of the patients described by Ellis[2] and Kuzman.[4]

Results

Incidence.—Sixty-seven patients had atrial fibrillation at the time of surgery. Of the 77 patients who had sinus rhythm prior to surgery, 36 (47%) developed atrial fibrillation postoperatively. This incidence is higher than that reported by other authors. Wood[5] reported 24%; Sellors,[6] 27%; Diamond,[7] 29%; Logan,[3] 31%, and Goodwin,[8] 38%.

Time of Occurrence.—Atrial fibrillation appeared during the first seven postoperative

Age Incidence and Sex Ratios of Patients in This Study Compared with Other Reported Series of Patients Subjected to Mitral Valvulotomy

Author	Age, Yr.						Male/Female Ratio
	10–19	20–29	30–39	40–49	50–59	60–69	
Baker[1]	3	25	47	21	4	0	1/2.3
Ellis[2]	3	73	183	188	49	3	
Logan[3]	1	22	36	27	14	0	1/4.9
Present study	1	23	51	56	14	0	1/3.2

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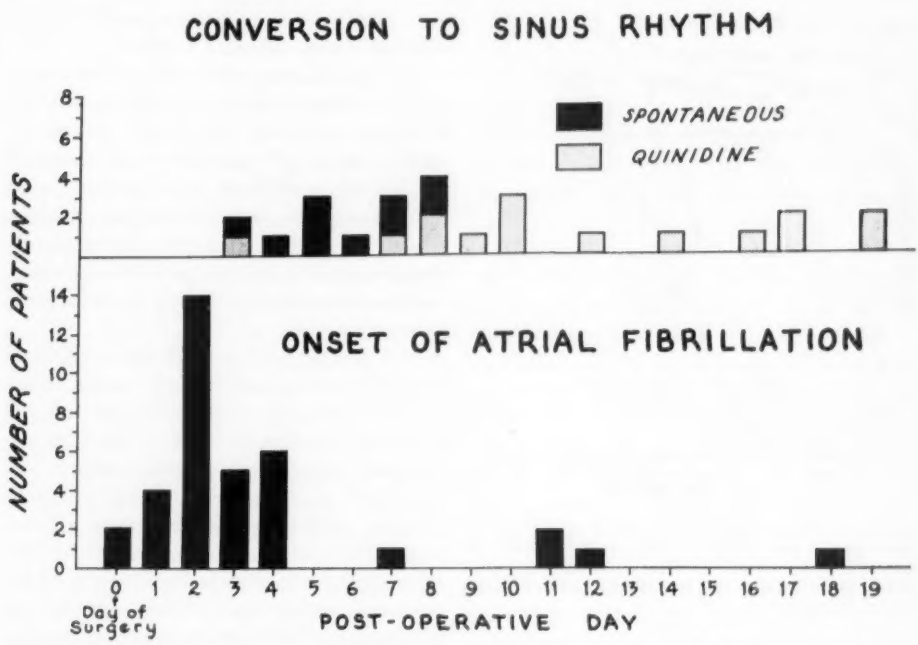

Fig. 1.—Graphic representation of occurrence of postoperative atrial fibrillation compared to time of spontaneous and quinidine-induced conversion. One patient not included on the graph was converted with quinidine 37 days postoperatively.

days in almost all (92%) of the 36 patients. This is in accord with the observations of others.[6-9] It is of interest that only two patients began to fibrillate on the day of surgery. Fibrillation appeared most frequently on the second postoperative day (Fig. 1). There was no relationship between the age of the patient and the day on which fibrillation appeared.

Effect on Patients.—With the appearance of atrial fibrillation, the ventricular rate increased, the mean ventricular rate of 31 patients being 142 per minute following the onset of the arrhythmia. These patients had all been receiving digitalis preparations. Six other patients not receiving digitalis fibrillated with ventricular rates of 124, 140, 160, 180, and 220 (mean, 168). One of these patients, a 52-year-old woman, developed peripheral vascular collapse, angina pectoris, and severe dyspnea when on the 20th postoperative day atrial fibrillation with a ventricular rate of 160 per minute appeared. The prompt administration of lanatoside C (Cedilanid) slowed the ventricular rate to 140 in two hours, and sinus rhythm appeared an hour later. In the patients who developed postoperative atrial fibrillation, no significant relationship between the ventricular rate and the age of the patient was noted. Aside from circulatory insufficiency and increasing pulmonary congestion occurring as consequences of the rapid ventricular rate, no other complications such as systemic or pulmonary emboli were noted after the onset of fibrillation. Those patients whose atrial fibrillation resisted efforts at conversion to sinus rhythm did not seem to be handicapped by this arrhythmia. The general results of valvulotomy appeared to be as good in these patients as in those who maintained or attained a sinus rhythm following surgery.

Factors in the Development of Fibrillation.—In an effort to determine what factors may play a role in initiating postoperative atrial fibrillation, the age of the patients was examined in relation to the incidence of

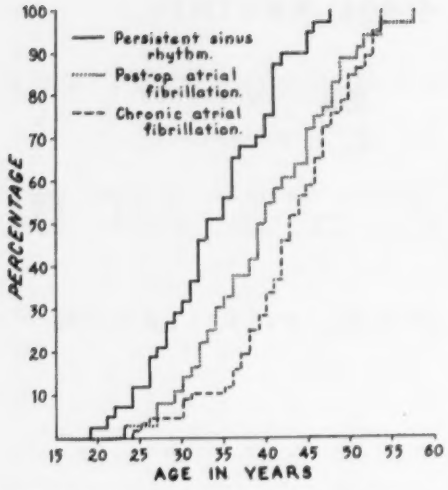

Fig. 2.—A cumulative distribution graph, showing the age distribution of patients who developed postoperative atrial fibrillation compared with those with persistent sinus rhythm and chronic atrial fibrillation.

fibrillation. As can be seen from the graph in Figure 2, the persons with persistent sinus rhythm are in a younger age group than those with chronic fibrillation who developed postoperative fibrillation. Using a 50% level of significance with the Kolmogorov-Smirnov test,[10] we find that the group with persistent sinus rhythm differs from the other two groups in being younger but that the postoperative fibrillation group and the chronic fibrillation group do not exhibit a difference large enough to be statistically significant at the 50% level. The mean age of patients who had fibrillation prior to surgery was 42.9 years, the mean age of those patients who maintained a sinus rhythm throughout their postoperative course was 33.8 years, and the mean age of those who developed atrial fibrillation postoperatively was 39.6 years.

These observations are in agreement with those of other workers who have demonstrated that the incidence of atrial fibrillation in rheumatic heart disease increases with the age of the patient [11] and in addition suggest that older patients with sinus rhythm are more likely to develop postoperative atrial fibrillation than younger patients.

It is well known that episodes of paroxysmal atrial fibrillation frequently precede the onset of persistent fibrillation during the natural course of rheumatic heart disease.[11] Of patients exhibiting postoperative atrial fibrillation, 28% gave a history of previous episodes of probable paroxysmal fibrillation, compared to 5% of those patients who maintained a sinus rhythm throughout their postoperative period.

The presence of a mild to a moderate degree of mitral insufficiency before fracture of the valve was noted in 28% of persistent fibrillators, 28% of patients developing fibrillation postoperatively, and 10% of patients with persistent sinus rhythm. In these patients an easily palpable regurgitant jet was present, and the mitral valve orifice admitted at least the tip of the operator's index finger. This apparent relationship of mild or moderate mitral insufficiency to persistent atrial fibrillation has been noted by others.[9,12] No apparent relationship between the size of the left atrium and the incidence of either persistent or postoperative atrial fibrillation was observed in our patients.

The presence of histologic evidence of rheumatic carditis as evidenced by Aschoff bodies in auricular biopsies was not associated with a higher incidence of either preoperative or postoperative atrial fibrillation. Indeed, an inverse relationship appeared to exist, for of the 12 patients who had positive biopsies, 8 maintained a sinus rhythm throughout their operative course. It has been demonstrated by others that positive auricular biopsies are commoner in younger patients in whom the incidence of fixed or of postoperative fibrillation is lower.[13]

No evidence was found to suggest that alterations in serum electrolytes, fever, or congestive failure were related to the appearance of postoperative atrial fibrillation. Measurements of serum electrolytes in many patients revealed no abnormalities except for occasional decreases in serum sodium.[14] All

patients had a moderate elevation of temperature beginning on the first to the third postoperative day, with gradual fall to normal. The onset of atrial fibrillation was not related to the appearance or amount of temperature elevation. Congestive failure appeared following the onset of atrial fibrillation in three patients and preceded its onset in two patients. Congestive failure increased following surgery in one patient who maintained a sinus rhythm. Auricular fibrillation in one patient followed an incident clinically characteristic of pulmonary infarction on the 18th postoperative day and converted a few hours later spontaneously.

Conversion.—After the onset of atrial fibrillation, slowing of the ventricular rate was achieved in most instances by the administration of additional digitalis glycosides. The amounts given varied considerably, but in many patients as much as one-half of a digitalizing dose given in one day was tolerated without evidence of toxicity, suggesting that these patients had previously not been fully digitalized. No arrhythmia due to digitalis overdosage occurred in the other patients except for the appearance of ventricular premature beats.

In 10 patients spontaneous return to normal sinus rhythm occurred. This took place in nine patients by the sixth postoperative day (Fig. 1), while one patient resumed sinus rhythm on the 18th postoperative day. No patient who had atrial fibrillation prior to surgery spontaneously reverted to sinus rhythm after surgery.

An attempt to restore sinus rhythm by means of quinidine was made in 23 of the 36 patients who developed atrial fibrillation postoperatively. Sinus rhythm was restored in 16 patients (70%) with an average of 2.5 gm. of quinidine. Conversion to sinus rhythm failed in seven patients (30%) who received an average of 7.7 gm. of quinidine. Failure or success of quinidine therapy did not appear to have any relation to age in this small group of patients. In most patients quinidine was not given until the seventh or eighth postoperative day to allow spontaneous conversion to occur and because it was belived that quinidine might be more effective in establishing sinus rhythm when the immediate effect of surgery upon the physiology of the body had disappeared. Restoration of sinus rhythm was achieved in this manner from the 6th to the 16th day in the 16 patients after surgery (mean, 11.3 days).

Quinidine was given postoperatively to 18 of the 67 patients who had atrial fibrillation prior to valvotomy. Sinus rhythm was restored in 7 (39%).

Inadequate information has made follow-up studies on these patients impossible. In some cases additional attempts at conversion were made, but an analysis of these patients was not attempted.

Comment

The high incidence of atrial fibrillation following mitral valvulotomy indicates the importance of mitral stenosis and associated atrial disturbance as factors in the production of the arryhthmia. Atrial fibrillation is an uncommon postoperative complication in patients who do not have rheumatic heart disease. In 64 consecutive thoractomies performed at the Stanford University Hospitals for pulmonary resections in patients without rheumatic heart disease there was only one patient (1.6%) who developed auricular fibrillation following surgery. Other authors have reported incidences of 3.5%, 6.4%, 12.2%, and 14.0% in older patients following lobectomy or pneumonectomy.[15-18] Auricular fibrillation is also an uncommon complication following surgery for congenital cardiac lesions.[19]

Patients with mitral stenosis who are most likely to develop postoperative atrial fibrillation appear to be those patients who also would have been most likely to fibrillate in the natural course of their disease. The three commonest factors observed in this study that appear to increase the possibility of fibrillation are (*a*) increasing age, (*b*) a previous history of paroxysmal atrial fibrillation, and (*c*) the presence of associated mitral insufficiency.

The mechanism by which surgery initiates atrial fibrillation in such a setting is unknown. The following factors may be important and worthy of discussion:

1. *Immediate Effect of Surgery.*—Trauma, anoxia, reflex effects upon the heart, blood loss, shock, and alterations in physiologic mechanisms which are maximal during surgery do not appear to be frequent causes of atrial fibrillation. The arrhythmia is occasionally encountered as a transient phenomen during surgery in some patients, but it began during surgery and persisted in only 1 of the 36 patients in this series, and only 2 other patients developed atrial fibrillation on the day of surgery. None of 56 patients studied by Fraser and Turner[9] developed fibrillation on the day of mitral valvulotomy.

2. *Activation of Rheumatic Carditis by Surgery.*—It had been believed by some that surgical procedures in patients with rheumatic heart disease may initiate an acute exacerbation of carditis. This seems an unlikely cause of postoperative atrial fibrillation for two reasons: (*a*) Histologic evidence of rheumatic carditis at the time of surgery is actually more commonly encountered in younger patients, who have a low incidence of fibrillation, than in the older patients, who more frequently fibrillate postoperatively. (*b*) Auricular fibrillation is not a frequent finding in rheumatic carditis in adults, changes in the P-R interval and heart block being commoner. Rogers and Robbins[20] studied 41 patients who came to autopsy with active rheumatic carditis proven by histologic study. Sixteen patients were over 20 years of age and had electrocardiograms recorded prior to death. Six had prolonged P-R intervals; two had complete heart block; two had P-R intervals at the upper limits of normal; three had normal records, and three patients, aged 38, 42, and 63, had auricular fibrillation of unknown duration.

3. *Traumatic Pericarditis.*—Fraser and Turner[9] suggested that the traumatic pericarditis following surgery may act as a stimulus to the onset of atrial fibrillation. Unfortunately there is little evidence to support this viewpoint and many reasons for believing that such an explanation is untenable. Electrocardiographic evidence of significant pericarditis following valvulotomy is rarely seen; atrial fibrillation rarely occurs during acute pericarditis of the so-called benign or idiopathic variety,[21,22] nor does it occur following surgery for congenital cardiac lesions, where the degree of pericarditis would be expected to be of a similar degree of severity as that following mitral valve surgery.[19]

4. *Increased Left Atrial Pressure* (Due to Postoperative Increase in Blood Volume).—Following mitral valve surgery urinary output is decreased, total body water is thereby increased, and serum sodium falls.[23,24] Blood volume increases as total body water increases. LeQuesne and Lewis[25] found a decrease in plasma protein concentration in 10 out of 13 patients during the first 24 hours after surgery from a mean of 6.8 gm/100 ml. to 6.3 gm/100 ml. This would correspond to a mean increase of 450 ml. in total blood volume. Moore and Ball have observed postoperative increases in blood volume of a similar magnitude.[26] Werkö and his co-workers determined the effect of increases in blood volume upon pulmonary artery pressures in patients with mitral stenosis. Blood volume was increased by infusions of dextran. A review of their data[28] indicates that a blood volume increase of 450 ml. would probably be accompanied by a 6 mm. of Hg rise in left atrial pressure. Such an increase in left atrial pressure may favor the development of atrial fibrillation by auricular distention.[27] This mechanism seems unlikely, since in most cases the left atrial pressure has been reduced by the valvulotomy, and presumably it would not become higher than prior to surgery even by hemodilution. Increasing pulmonary congestion or congestive failure does not commonly occur following valvulotomy. It was noted in only five patients in this series (3.5%), and in these patients it preceded the onset of atrial fibrillation in only two patients. Arm-to-tongue circulation times

were measured in five patients on the day preceding surgery and again on the third or fourth postoperative day. Four patients with initial values of 14, 21, 23, and 32 had prolongations of three, one, two and one seconds, respectively. One patient with mitral regurgitation in whom no valve fracture was done had an initial circulation time of 23 seconds, which was lengthened to 35 seconds on the fourth postoperative day.

5. *Postoperative Alterations in Serum or Intracellular Electrolytes.*—It has been demonstrated by several workers that accompanying the hemodilution mentioned above there are often striking changes in electrolyte concentrations following surgery. Potassium moves out of the cells, serum potassium may be increased transiently, and potassium excretion is increased. Simultaneously sodium and water excretion are impaired, sodium probably moves into the cells, and serum sodium is usually lowered.[23,24] Analyses of muscle biopsies have demonstrated as decrease in intracellular potassium during this period.[29] As illustrated in Figure 3, these changes become most marked on the second and third postoperative days, and the normal state is usually restored by the seventh postoperative day. Atrial fibrillation in the patients in this study appeared most frequently on the second postoperative day and the tendency to fibrillate diminished after the seventh day, corresponding to the intensity of the above electrolyte alterations. It is quite possible that a decrease in intracellular potassium content in the favorable setting of mitral stenosis initiated the atrial fibrillation, despite little evident change in the serum levels of potassium. It has been

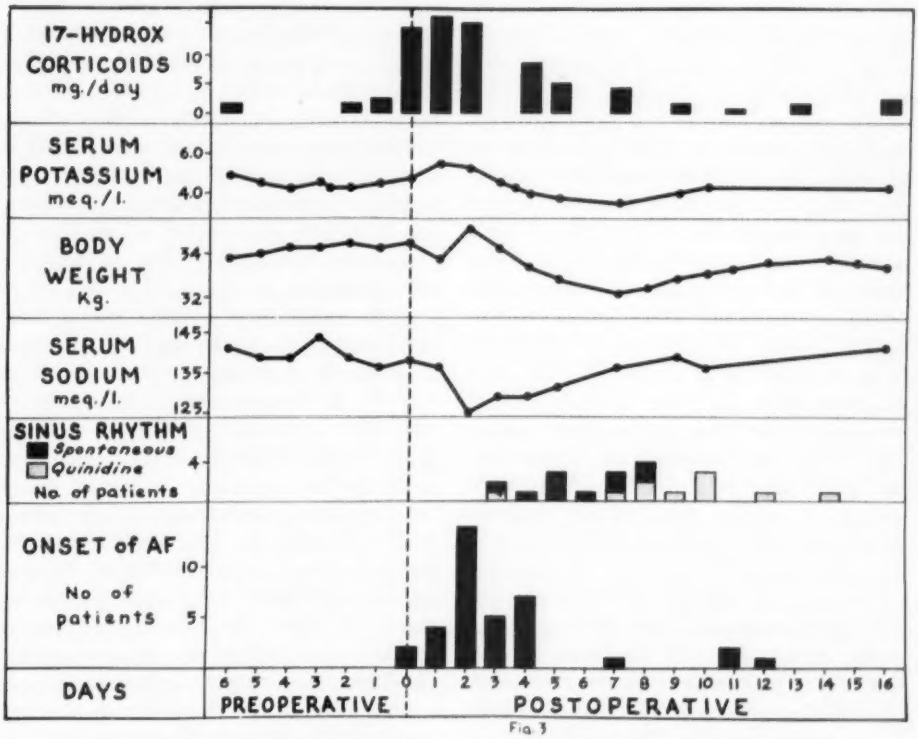

Fig. 3.—Summary of postoperative alterations in electrolytes and body weight correlated with date of onset of atrial fibrillation following valvulotomy (Electrolyte data replotted from Wilson et al.,[28] Fig. 1).

pointed out that the mere presence of normal levels of body solutes or water does not guarantee intact total amounts,[30] and the changes in electrolyte and water metabolism summarized above may not have been accompanied by significant changes in serum electrolyte concentrations. Brooks[31] has stated: "Small changes in the level of K+ ions may have profound effects on excitability and electrical activity of both isolated and in situ hearts, especially when the level of Ca++ remains constant." These changes greatly increase the vulnerability of the heart to fibrillation. Armitage, Burn, and Gunning have demonstrated a striking increase in cardiac vulnerability to shock-induced atrial fibrillation in the isolated heart by lowering the potassium content of the perfusate.[32] Burn and his co-workers have also demonstrated that shock-induced atrial fibrillation maintained by acetylcholine infusion in the heart-lung preparation can be restored to normal rhythm by the infusion of KCl. Part of the action of acetylcholine in such an experiment may be to increase cellular permeability to K+ with an efflux of K+ from the cell. This is reversed or prevented by potassium infusion.[33] However, there are several reasons to suggest that atrial fibrillation was not caused by a decrease in cellular potassium. Atrial fibrillation is not commonly associated with potassium depletion.[19,34,35] Potassium depletion usually is accompanied by an increased sensitivity to digitalis.[36] This was not apparent in this study following mitral valvulotomy, and most patients were able to tolerate increased amounts of digitalis following the onset of fibrillation without toxic effects. A careful study of electrocardiograms taken daily following valvulotomy in 20 patients failed to reveal any alterations in the T waves or apparent Q-T intervals suggesting transient potassium deficiency.

The data obtained in this study are not sufficient to indicate the probable mechanism by which surgery initiates atrial fibrillation in susceptible patients. The mechanism appears most effective on the second postoperative day, and its effect has subsided by the seventh postoperative day. This suggests that it is related to the total physiologic response of the body to surgery and not directly to the trauma of the operative procedure.

From the limited data obtained in this study, it would appear that digitalis in full digitalizing doses should be given to all patients prior to mitral valvulotomy. Should atrial fibrillation appear, the ventricular rate will thus be lower, and sudden circulatory collapse or pulmonary congestion may be avoided. This is suggested by the fact that most patients required additional digitalis to slow their ventricular rate following the onset of atrial fibrillation and that four out of six patients not receiving digitalis had very rapid ventricular rates following the onset of atrial fibrillation. One of these patients developed peripheral vascular collapse. Whether atrial fibrillation is more likely to appear in patients who are receiving digitalis than in those who are not cannot be answered by our data. This arrhythmia may rarely be caused by digitalis overdosage.[38] When atrial fibrillation does appear the ventricular rate should be slowed if it is rapid by the administration of additional digitalis. A quick-acting parenteral preparation should be used if the ventricular rate is high and pulmonary edema or shock appears imminent.

In the majority of patients whose atrial fibrillation appears after surgery, quinidine in relatively small doses will restore sinus rhythm. It therefore would seem wise to attempt to restore sinus rhythm by quinidine in every patient who develops postoperative atrial fibrillation before the patient leaves the hospital. Quinidine can be successfully used in a smaller percentage of patients who had preoperative atrial fibrillation. Because spontaneous return to a sinus mechanism may occur before the seventh postoperative day in nearly 30% of patients who develop fibrillation after surgery, quinidine administration may be withheld during the first postoperative week to allow this to occur. It is also possible that for the same reason quinidine may be more effective at this time

than when given immediately after the onset of fibrillation. These conclusions are in general agreement with those of other authors.[3,5,7-9] Prophylactic quinidine started either before or immediately after operation appears to be of no value in preventing the onset of atrial fibrillation.[5-7]

Summary

Atrial fibrillation appeared following mitral valvulotomy in 47% of 77 patients who had a normal sinus rhythm prior to surgery. The onset of postoperative atrial fibrillation was commoner in older patients, in those who had had prior episodes of atrial fibrillation, and in those who had some degree of associated mitral insufficiency. Fibrillation appeared most frequently on the second postoperative day and rarely on the day of surgery. Spontaneous resumption of sinus rhythm occurred in 10 patients, and quinidine restored sinus rhythm in 16 patients, leaving 10 who had persistent postoperative atrial fibrillation. The mechanisms responsible for the onset of atrial fibrillation are unknown, but the arrhythmia occurred at the time when postoperative alterations of body fluids and electrolytes were maximal. A decrease in intracellular potassium is probably not the cause, however. Since the ventricular rate is high in patients not receiving digitalis, and since additional digitalis was needed to slow the ventricular rate of most patients who developed postoperative atrial fibrillation, all patients should probably be fully digitalized prior to valvulotomy. Since spontaneous resumption of sinus rhythm occurs in many patients, quinidine may be withheld until the seventh postoperative day. It also may be more effective at that time, since the factors responsible for the onset of atrial fibrillation have by then apparently diminished.

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An Inquiry into "Bangungut"

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There have been reports in the lay press [1,2] as well as in medical literature of sudden unexplained deaths during sleep among Filipinos. The victims are generally young (between 25 and 40 years of age) robust men without manifestations of any prior illness, who go to sleep after eating a heavy meal and while asleep are observed to cough, choke, gasp, groan, scream, yell, or struggle and then suddenly die without waking up from their sleep. In a known patient [3] who woke up but who died when he returned to sleep the same night, headache and abdominal pain were complained of.

The incidence of these deaths is greater among the laboring class [4,5] than among businessmen and professionals, and although in Hawaii other Orientals form a sizeable group, the malady seems to be confined to Filipinos. Of the 30 deaths reported in the city of Manila in 1955, 26 were among Filipinos and 4, among Chinese. Slightly more deaths are reported during the months of March, June, and December, although they are reported throughout the year.

The usual postmortem findings are cyanosis, generalized visceral congestion, subpleural and subepicardial petechial hemorrhages, gross and microscopic hemorrhagic pancreatitis, frequently a stomach dilated with partially digested food, marked rigor mortis, dilatation of the right ventricle of the heart, pulmonary congestion, and edema.[5-8] Decreased coagulability, laking, hyperglycemia, and low carbon dioxide tension have been observed in blood samples taken post mortem.[9]

Though "bangungut" is the Tagalog * word for nightmares, the term as used in this paper refers to these unexplained deaths. The term was chosen from common usage for convenience and not from agreement with the common belief that nightmares cause these deaths.

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* See Glossary appended.

Theories

Various theories have been advanced to explain the sudden deaths—some based on necropsy findings, others merely gratuitously offered.

1. *Mechanical Theory* (Sison).—This theory assumes that the distention of the stomach due to the preceding heavy meal embarrasses the heart either by direct mechanical pressure or reflexly through the vagus nerve. Majoska cites Sison's observation that similar cases of death occurred in swimmers who drowned after plunging into cold water after having indulged in a heavy meal. Lara [9] believes that the embarrassment to the heart and respiration caused by the full stomach causes the nightmares, while metabolism of large amounts of rice eaten results in the production of more carbon dioxide, which accounts for the decreased carbon dioxide combining power of the blood.

2. *Cardiac and Beriberi Theory.*—This theory assumes that the person has a subclinical form of heart disease or cardiac beriberi and that the struggling of the person during the nightmare precipitates death. The suddenness of the death and the findings of dilated right ventricle have been advanced to support the theory. Santa Cruz,[7] however, points out that in recent years, with improved nutrition, the incidence of hypovitaminosis B_1 has decreased but the incidence of "bangungut" has increased. Majoska also pointed out this discrepancy in incidence between "bangungut" and beri-

beri in Hawaii and adds that "malnutrition is definitely not a factor since the Filipinos affected are remarkably well-developed."

3. *Nightmare Theory.*—The common belief among Filipinos is that these persons died of nightmares. The belief is probably based on the observation that those who experience nightmares also groan, moan, and struggle during their sleep. Since almost all who died never woke up from their sleep, it is not certain whether they did have nightmares or not; but one case reported by Lara woke up and remarked of having such nightmares, then slept again and died. The nightmare is also believed to be the trigger mechanism in the cardiac theory and the corticoadrenal exhaustion theory.

The laity believes that if the victim could only be wakened from his sleep, he could be saved. Various ways have been advocated to rouse supposedly prospective victims.

Manalang [6] thinks that the pulmonary hemorrhages seen at autopsy are responsible for the death and that these hemorrhages are produced by the violent movements of the person when he has the nightmare.

4. *Toxic Theory.*—This theory presupposes the formation in the gastrointestinal tract of a toxic substance from the food eaten (or the toxic substance may be preformed in the food). Majoska disclosed that the person who died did not eat any unusual food and that other persons had partaken of the same food without apparent ill-effects. Santa Cruz dismisses this theory by stating that "the toxic theory can explain the pathology of the acute hemorrhagic pancreatitis better than its action upon the heart." He did not elaborate on this statement nor on the following: "In three of the autopsies, I fed the stomach content to dogs; but nothing happened to the animals, not even a slight change in their behaviour."

Alcoholic intoxication, curare, and heavy-metal poisoning have been eliminated as possible causes.[5]

5. *Acute Pancreatitis Theory.*—While the findings of hemorrhagic or necrotizing pancreatitis seemed to be the only pathologic evidence which could account for the deaths, this theory has not received much support, owing to the fact that not all the victims show pancreatic lesions, and, besides, it is known that acute pancreatitis does not produce such a dramatic death as is observed in these "bangungut" cases. In support of this theory, Gerundo [10] injected trypsin intravenously and claims to have reproduced the findings in "bangungut." Since acute pancreatitis is reported among peoples of other countries, the theory does not satisfactorily explain why male Filipinos are predominantly affected by "bangungut." It has not been ascertained whether the pancreatitis is a cause or an effect.

Other possible causes thought of were intestinal fluke infestation [6]; allergy [7] (Vitug); corticoadrenal exhaustion,[8] or stress and strain (Garcia, Liboro [11]).

The experiments reported in this paper were performed in an attempt to test some of these theories.

Effects on the Circulation of Mechanical Distention of the Stomach

Working on the assumption that death may be caused by a fatal cardiovascular reflex arising from an overly distended stomach, the author, together with Dr. Francisco T. Roque, during the war years of 1943-1944, placed balloons inside the stomachs of dogs and observed the effects of inflating the balloon on the blood pressure and heart rate. The records of these previous experiments were not saved from the ravages of the war, but recently these experiments were repeated. The typical results are shown in Figure 1. In the unanesthetized dog there was a slight rise in arterial pressure, while in the anesthetized animal there was either a rise or a fall in mean arterial pressure when the intragastric pressure was raised. The rise in mean arterial pressure was not due to compression of the aorta by the bloated stomach, since clamping the aorta itself did not produce such a change. As in our earlier experiments no fatal cardiovascular reflex could be demonstrated.

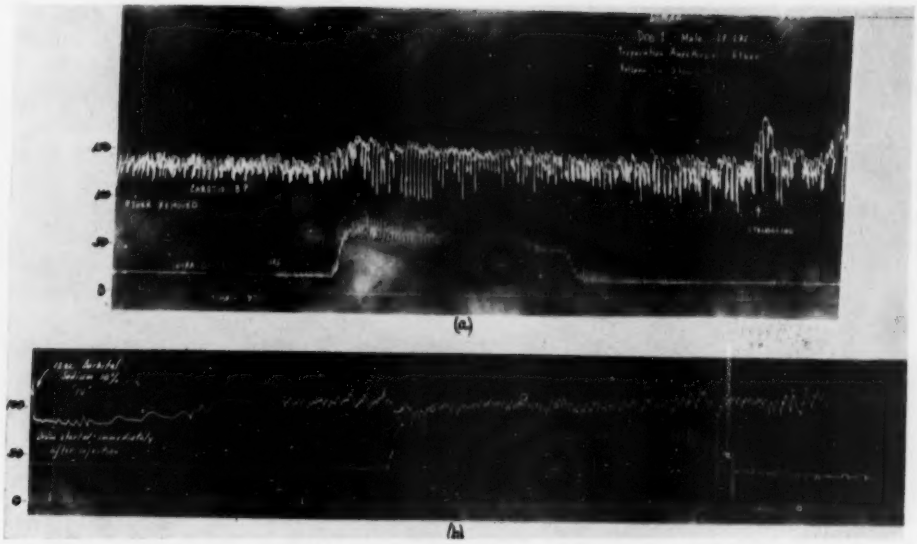


Fig. 1.—Gastric distention and blood pressure. (*a*) In an unanesthetized animal. (*b*) In an anesthetized animal. Upper tracings indicate carotid blood pressure; middle tracings, intragastric pressure; lower tracings, "0" pressure and time line.

Though gastric distention may not directly cause death, subsequent observations reported in this paper suggest the possibility that a full stomach may contribute to the death of an animal, not through its effects on the circulation but by decreasing respiratory volume.

Effects on the Blood Pressure and Respiration of Certain Articles in the Filipino Diet

Because of the visceral congestion and the absence at autopsy of anatomical findings to account for the sudden death, shock was suspected as a cause of death. It is known that there are certain Filipino foods which are "makati," that is, they cause itchiness at the tongue and lips, with swelling and wheal formation in these areas. It was thought possible that these foods may contain a substance which increases capillary permeability and thereby produces circulatory shock. The experimental investigations were sparked by a personal experience in which I had a nightmare and, on recalling what had been eaten the previous meal, remembered relishing "pacsew na dilis" with a sauce of tomatoes, onions, "wansoy," and "patis"—a combination typically Filipino. "Patis" is known to produce wheals on the lips and tongue.

The preliminary experiments with "patis" proved so interesting that other dietary articles were subsequently tested.

The experimental methods employed follow: mongrel dogs, male or female, were placed under intravenous barbital sodium anesthesia at a dose of 1.5 to 2.0 cc. of a 10% solution per kilogram of body weight. When unanesthetized animals were needed, surgical procedures were accomplished under ether anesthesia and the ether later withdrawn. Carotid blood pressure was recorded on a kymograph with a mercury manometer while respiration was recorded with a corrugated-rubber stethograph. In later experiments, a spirometer was connected to the tracheal cannula to record respiratory volume. Intravenous injections were made through a femoral cannula connected to a Murphy drip and to a burette filled with isotonic saline solution; intragastric admin-

The Fall in Mean Arterial Blood Pressure Produced by Intravenous Injection of Various Food Extracts

A. Foods producing a fall of 50 mm. of Hg or more
  0.5 cc. 1:10 "tuyo"
  0.5 cc. 1:10 "patis"
  0.5 cc. 1:10 "balbacua"
  1.0 cc. 1:10 squid, dried, fried
  1.0 cc. 1:10 pork, salted
  1.0 cc. 1:10 "dilis," fried
B. Foods producing a fall of 25-50 mm. of Hg
  1.0 to 2.0 cc. 1:10 "tunsoy," tinapa
C. Foods producing a fall of less than 25 mm. of Hg
  1.0 to 3.0 cc. 1:10 soy sauce
D. Foods not causing any fall in blood pressure
  1.0 to 2.0 cc. 1:10 extract of
    Oyster, steamed
    Shrimp, dried
    "Tunsoy," pacsew
    Crab, boiled
    Chicken, "nilaga"
    "Bangus," fried
    Pork chops, fried
    Beef, "nilaga"
  1.0 to 2.0 cc. saturated solution of common table salt

istration was by means of a stomach tube passed through the mouth. Extracts of foods were prepared by triturating a given weight of the material with known volumes of water and then filtering through ordinary filter paper. A total of 11 dogs were used in these experiments.

The Table shows the magnitude of the fall in mean arterial pressure produced by intravenous injection of the various food extracts tested. The fall in pressure is not unlike that produced by histamine, from which the animal recovers rapidly. The vasodepressor substance (or substances) is stable at room temperature. Vigorous boiling for five minutes did not destroy it. Another significant observation is that the vasodepressor material is found in larger concentrations in preserved (dried, salted, or smoked) rather than in fresh foods and more frequently in fish products.

For further studies, the choice as to which food should be used fell on "patis" because (1) it is a ready-made and commercially available aqueous extract of a food that is commonly eaten by many Filipinos ("bagoong"); (2) it is not only available in large quantities, but its preparation is more or less standardized, and (3) being a liquid, it may be easily introduced by means of a stomach tube.

Figure 3 shows a typical experiment in which "patis" was given through a stomach tube. An immediate fall in mean arterial pressure occurs within one minute after administration of "patis," but the animal gradually recovers. Shock levels of blood pressure may be maintained by periodic administration of small amounts of "patis." In one dog, persistent low levels of arterial blood pressure resulted in transient irregularities of heart action. Of six experiments in which the intention was to kill the animal, only four died. In two of these, intravenous barbital was given at the start of the experiment; in the other two, intravenous barbital was given only after it was evident that the animals would not succumb to "patis" alone. Two other animals given the same dose of barbital sodium but not given "patis" survived. The manner of death was identical whether "patis" was given intragastrically or intravenously. Death in all the animals was not due to cardiac nor to circulatory failure but due to respiratory failure—the respiratory movements definitely stopping first, only to be followed by the usual asphyxial rise in arterial blood pressure, terminating in death. In two animals during the terminal fall in arterial pressure, attempts to breathe were accompanied by a secondary rise in blood pressure. Respiratory failure was not due to shock, because in one dog (Dog 4), the blood pressure was relatively unaffected and was definitely above shock levels when respiratory failure ensued.

Though a gradual decline in the magnitude of respiratory movements was evident in the stethographic records, the terminal attempts to breathe exhibited by some animals show that respiratory failure was not due to depression or paralysis of the respiratory center itself but must be due to some condition preventing or the absence of another factor allowing the full activity of the center. During the early stages of each experiment, periodic deep inspirations were noticeable in the stethograph records. These deep inspirations became less frequent or disappeared as death of the animals drew near and the blood became darker. A change to a brighter tint in the color of the blood in the carotid cannula may be noticed after the occurrence of one or two such deep inspirations. In one

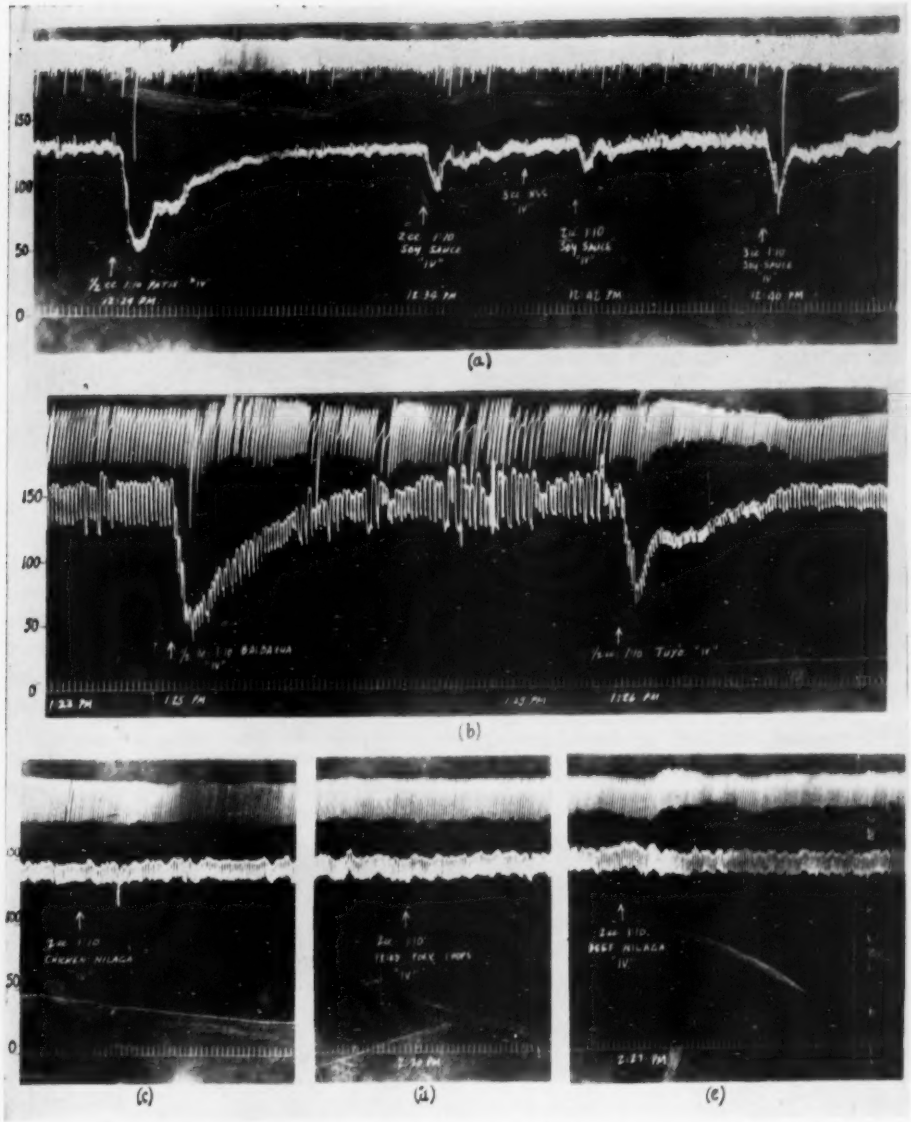


Fig. 2.—Effect of some foods on blood pressure. (*a*) Patis, soy sauce, normal salt solution. (*b*) Balbacua, tuyo. (*c*) Chicken nilaga. (*d*) Fried pork chop. (*e*) Beef nilaga. Upper tracings indicate respiratory movements; middle tracings, carotid blood pressure; lower tracings, "0" pressure and time line.

dog which was not under anesthesia, a dose of "patis" greater than a usually fatal one did not kill the animal, while in another (Dog 8), it appeared that the dog would survive the intragastric administration of "patis" until 10 cc. of barbital sodium (10% solution in water) was given intravenously to put the animal to sleep. This dog weighed 14 lb. Barbital sodium alone, at a dose of 1 cc. per kg. body weight of the 10% solution intravenously, did not kill four other animals. It seems, therefore, that the

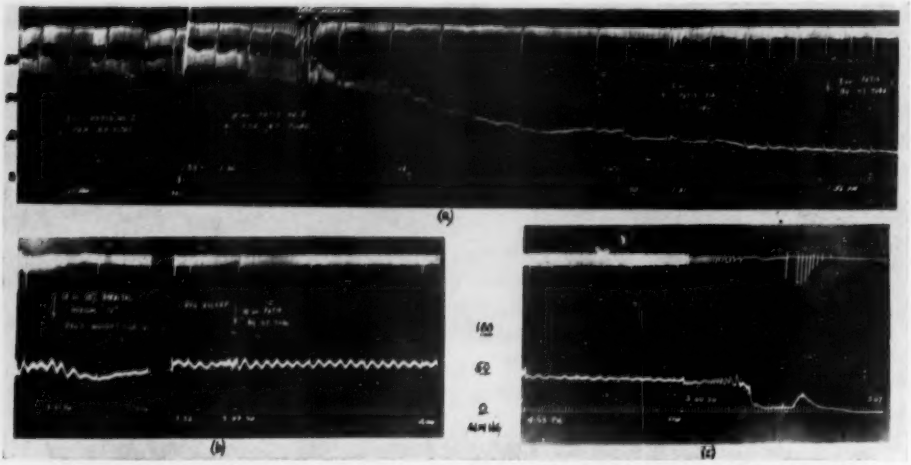
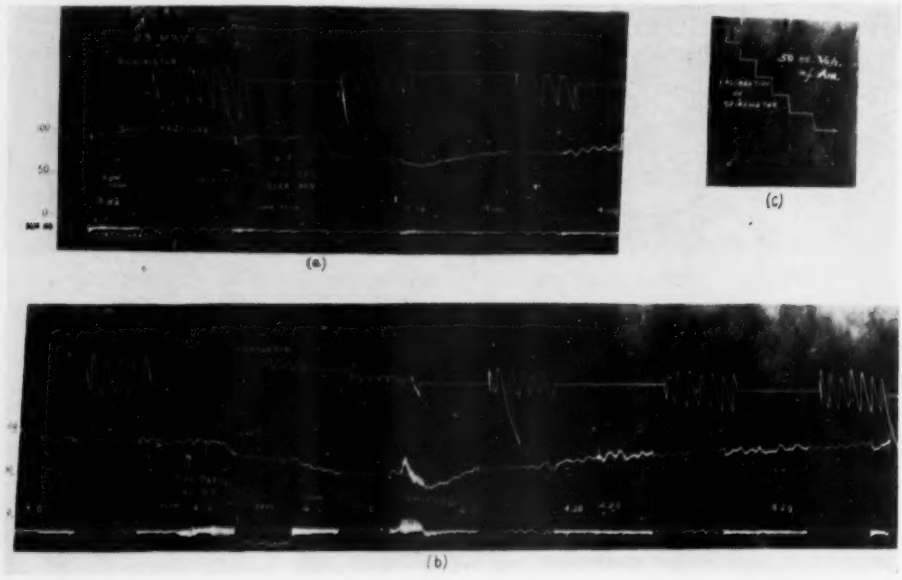


Fig. 3.—Typical effects of "patis" on respiration and blood pressure. (*a*) With ether withdrawn, two 5 cc. doses of patis were given initially intragastrically. (*b*) Barbital sodium given to put the animal to sleep approximately two hours after the start of the experiment. (*c*) Death of the animal one and one-half hours after the barbital sodium administration. Note cessation of respiration before the terminal drop in blood pressure and the secondary rise in pressure when the animal made agonal attempts to breathe. Upper tracings indicate respiration; middle tracings, carotid blood pressure; lower tracings, "0" pressure and time line.

Fig. 4.—Effects of barbital sodium and of patis on respiratory volume. Drum speed was accelerated every time spirometric measurements were done. (*a*) Effect of intravenous injection of 10 cc. 10% barbital sodium. (*b*) Effect of 10 cc. of patis by stomach tube. (*c*) Calibration of spirometer, showing movements produced by 50 cc. volume changes. Tracings, from the top downward, indicate respiratory volume, carotid blood pressure, "0" pressure, respiratory movements.



effects of "patis" combine with the effects of the barbital sodium to produce an asphyxial death.

Spirometric measurements of respiratory volume disclose that there is a tremendous decrease in tidal air volume after intragastric administration of "patis" (Fig. 4). It appears that this decrease in respiratory volume produced by "patis" may be corrected by certain pulmonary reflexes in the unanesthetized animal. In the anesthetized animal, however, the reflexes are depressed or inhibited, and the animal gradually goes into asphyxia or anoxemia, which ultimately affects the respiratory center.

Postmortem Fndings in the Experimental Animals

As soon as the heart stopped beating, the animals were opened for the usual postmortem examination. Grossly, what were immediately noticeable were the pulmonary congestion, edema, and sometimes emphysema; a heart distended with blood; visceral congestion with submucous gastric hemorrhage in one dog, and dark-colored blood evident in the cannula and mesenteric vessels.

Dr. L. Gomez, head of the pathology department of the institute, summarized the histological findings as follows: "The most constant features are the changes in the lungs which are either congestion, atelectasis or interstitial bronchopneumonia. The liver shows partial congestion and in one case, small foci of polynuclear leucocytes. The pancreas sometimes shows interstitial hemorrhages which are likely due to manipulation but there is no inflammatory reaction or necrosis. The kidney shows no congestion but possibly cloudy swelling. The spleen shows some congestion of the sinusoids, although it is difficult to appreciate because of its great cellularity which might be normal in the dog. The stomach, in one dog, shows markedly congested mucosa and in another, a marked amount of mucus secretion. The adrenal in one dog (Dog 4) shows polynuclear leucocyte infiltration in the cortex."

Summary

The usual observations in sudden death during sleep among young Filipino men are mentioned, and the theories advanced to explain these deaths are listed.

No fatal cardiovascular reflex could be elicited by distending the stomachs of dogs with a balloon.

There is a potent vasodepressor substance (or substances) in certain articles of the Filipino diet. The substance is thermostable and is present particularly in fish subjected to partial decomposition.

One of the fish products, "patis," produces death in experimental animals anesthetized with barbital sodium, whether it is given intragastrically or intravenously.

Death is apparently produced through reduction of the respiratory volume of the animal producing a gradual asphyxia, which may terminate fatally when pulmonary reflexes are depressed by the anesthesia.

It is not certain whether the vasodepressor material is the same substance which causes also the decreased respiratory volume.

Except for the absence of histological evidences of acute hemorrhagic or necrotizing pancreatitis, the postmortem findings in the experimental animals are similar to those seen in human "bangungut."

Glossary†

Ba-go-*ong*: Fish or small shrimps salted and with litle or no water added and allowed to decompose in a vat for several weeks; usually sautéd before serving.

Bal-ba-*cua*: Fish salted and preserved with its scales on; served fried or broiled.

Bang-*us*: milkfish.

Dil-is: A species of small fish.

He-be: Small dried shrimps.

Ni-*la*-ga: A dish prepared by boiling in water with some vegetables and whole black pepper thrown in.

Pac-se-*w*: A dish prepared by cooking in vinegar.

Pa-*tis*: A sauce made from fish; the supernatant fluid derived from "bagoong."

Ti-na-*pa*: Smoked fish.

Tun-*soy*: A species of fish.

Tu-*yo*: Salted dried fish.

† The stress is on the italicized syllable.

Wan-*soy*: A leafy plant used for flavoring.
Ta-*ga*-log: The Philippine national language.

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Benign Purpura Hyperglobulinemica

Report of a Case

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In 1943, Waldenström, reviewing a large number of cases with hyperglobulinemia found three patients with a characteristic syndrome which he designated as "purpura hyperglobulinemica."[1-3]

This syndrome, seen predominantly in females after puberty, manifests itself by crops of petechiae or a purpuric rash, usually on the lower extremities, appearing at irregular intervals and occasionally preceded by a sensation of tenderness or even definite swelling of the involved limbs. The onset of the purpura has been related to overexertion or infections in a few cases. It usually disappears after a few days, and areas of brownish pigmentation may remain.

In the majority of cases, physical examination is noncontributory, although parotitis, conjunctivities, moderate generalized lymphadenopathy, hepatosplenomegaly, and tenderness of the lower extremities may be irregularly present.

Most of these patients have a normochromic normocytic anemia and an elevated sedimentation rate. Routine coagulation tests are normal, although Wilson et al.[4] reported two cases who had moderate thrombocytopenia. The tourniquet test may be positive. Ultracentrifugation of the serum shows an increase in the γ-globulin fraction due to an elevation of the S-7 component.

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Since Waldenström's initial papers, other cases with this syndrome have been observed in Europe.[5-14] However, only a few reports have appeared in the American literature.[4,15,16] This paper describes a patient with typical purpura hyperglobulinemica of three years' duration.

Report of a Case

The patient, a 36-year-old white woman, was first seen in June, 1955. In 1952, the patient developed a sensation of tenderness in the right knee, associated with a feeling of heat and a slight reddish discoloration. This was transitory, but approximately one month later, she noticed "tiny red spots" on the skin of both lower extremities, which disappeared slowly. Since then, she has noticed similar spots, located over the distal portions of her lower limbs, appearing at varying intervals of time. No relation of the occurrence of the purpura to menstrual cycles, foods, or drugs could be elicited. Prolonged standing, overexertion, and kneeling for prayer definitely precipitated the purpura. Swelling of the ankles was often associated with the petechiae. Past and family histories were noncontributory.

Physical examination.—Multiple petechiae were noted on the legs and ankles. They were sharply demarcated, measured 1 to 2 mm. in diameter, and did not disappear with pressure. No inflammatory signs were noted. The lower limbs showed multiple areas of a mottled, brownish skin pigmentation (Fig. 1). Liver, spleen, and kidneys were not palpable. The remainder of the examination was negative.

Laboratory Studies.—Urinalysis was negative. Hemogram was normal except for an elevated sedimentation rate (100 mm/hour, Westergren method, Table 1). Platelet count, bleeding time, clotting time, tourniquet test, and prothrombin were within normal limits. Five lupus erythematosus preparations were negative. Marrow aspiration was essentially normal save for a slight increase in plasma cells of 5% (500 cells counted). Liver-function studies revealed only an elevation

Fig. 1.—Photograph of patient's legs. Note the brownish skin pigmentation, more pronounced about the ankles. Scattered purpuric and petechial areas are also seen.

of the cephalin-cholesterol flocculation after 48 hours.

Roentgenograms of the chest and bones were normal. An electrocardiogram was within normal limits. No cryoglobulins were found. Ultracentrifugation of her serum was negative for macroglobulins.*

elevated sedimentation rate, and an increase in γ-globulin without detectable underlying disease, are the salient features of benign purpura hyperglobulinemica. Our patient did not have anemia; this has been found in only one previously reported case.[15] The finding of an abnormal cephalin-cholesterol flocculation test in the presence of otherwise normal liver function studies reflects, we believe, the increase in γ-globulin and not liver disease.[17,18]

Purpura hyperglobulinemica has been classified into two main groups: primary and secondary.[11,13] In the secondary type, hyperglobulinemia and purpura are found accompanying an underlying disease process, such as cirrhosis of the liver, sarcoidosis, lipoid nephrosis, leukosarcoma, multiple myeloma, and rheumatoid arthritis. In the primary form, there is usually a history of

TABLE 1.—*Laboratory Data*

Urinalysis		Hemogram	
pH	5.0	Hb.	13.7 gm./100 cc.
Specific gravity	1.016	RBC/cu. mm.	4,200,000
Albumin	Neg.	WBC/cu. mm.	6,550
Sugar	Neg.	C. I.	1.0
Acetone	Neg.	MCV	95 cu. μ
Bence-Jones protein	Neg.	Sedimentation rate	
Microscopy	Neg.	per hour (Westergren)	100
Bile	Neg.	Differential count	Normal
Urobilinogen	Trace		
Clotting Studies		**Liver-Function Tests**	
Platelets (Dameshek)	530,000	Bilirubin	0.5 mg./100 cc.
Bleeding time (Duke)	1½ min.	Serum cholesterol	129 mg./100 cc.
Clotting time (Lee-White)	8 min.	Esterified	91 mg./100 cc.
		Per cent esterified	76
Prothrombin time		BSP	0.4 mg./100 cc.
(Quick)	11 sec.	Cephalin-cholesterol flocculation	4+

L. E. preparation (clotted blood): Neg.
Bone-marrow aspiration: normal except for increase in plasma cells (5%)
Cryoglobulins: Neg.
Macroglobulins: Neg.

The serum protein was 8.4 gm. per 100 cc., of which 2.5 gm. was albumin and 5.9 gm. was globulin. The γ-globulin fraction was 2.9 gm. per 100 cc. This value is far above the normal range in our laboratory (normal, 0.7 to 1 gm. per 100 cc.). Tabulation of the protein fractions and chemical and electrophoretic methods is found in Table 2. The electrophoretic pattern of the serum protein is shown in Figure 2.

Comment

The history of recurrent purpura over the lower extremities, the presence of an many years' duration, and no systemic disease is found. Our case falls into this last category.

The differentiation of purpura found in cryoglobulinemia and macroglobulinemia must be made. Cryoglobulinemia is sometimes found with hyperglobulinemia in the following conditions: multiple myeloma, systemic lupus erythematosus, kala-azar, malaria, polyarteritis nodosa, subacute bacterial endocarditis, lymphatic leukemia, and lymphosarcoma. The purpura associated with cryoglobulinemia appears after expos-

* Dr. Lars Larson, University of Chicago, performed the ultracentrifugation studies.

TABLE 2.—*Protein Fractionation*

Fraction	Chemical Method, Gm./100 Cc.	Paper Electrophoresis, Gm./100 Cc.
Albumin	2.9	2.5
α-globulin	1.2	1.3
β-globulin	1.7	1.7
γ-globulin	2.6	2.9

ure to cold and with Raynaud's phenomenon and urticaria. Skin ulcerations are common. These features were absent in our patient, and we were unable to demonstrate cryoglobulins.

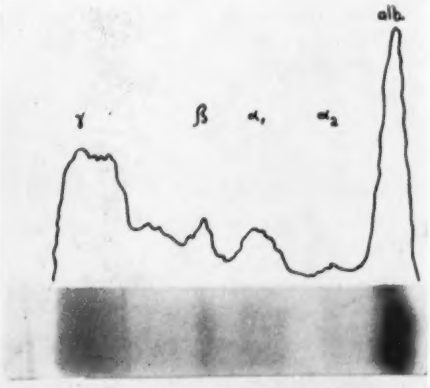
Skin purpura is a very rare clinical manifestation in macroglobulinemia,[19] however, it has been reported in a case by Tischendorf and Hartmann.[20] A negative distilled-water test and inability to detect macroglobulins on serum ultracentrifugation definitely exclude this disease in our patient.

An adequate pathophysiologic explanation for purpura hyperglobulinemica is lacking. Waldenström[3] suggests the possibility of a chronic benign virus infection acting as a continuous stimulus to antibody formation, leading to increased serum globulins. He also put forth the hypothesis that a deficiency in some globulin fractions necessary for the maintenance of normal capillary resistance may be the cause of the disease.

Other authors[8,14,16,21] invoke an allergic disturbance producing an alteration in the γ-globulin which, in turn, affects the status of the capillary endothelium. Skin and muscle biopsies in two cases reported[16,22] have revealed a vasculitis.

There is no adequate treatment for this condition at the present time. Steroids have been used without effect.

Fig. 2.—Serum protein electrophoresis patterns. (An error was made in preparing the drawing and α_1 and α_2 are reversed.)



Summary

The case of a 36-year-old white woman with a three-year history of recurrent purpura over the lower limbs, leaving a brownish pigmentation on the affected skin, associated with elevated γ-globulin concentration and a rapid sedimentation rate, is reported. No underlying systemic disease was found. We believe that this patient represents a case of benign purpura hyperglobulinemica.

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Is There an Entity Primary Pulmonary Hypertension?

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The question as to whether essential or primary pulmonary hypertension actually exists has not been conclusively settled. This condition has been defined by Dresdale and his associates as an elevation of pulmonary artery pressure without demonstrable cause.[1] These authors compare primary pulmonary hypertension with essential systemic hypertension and point out that in the latter there is increased tonus of the precapillary arterioles, while in the former there would seem to be a state of increased tonus of the small pulmonary arteries. They also state that the respective vascular beds, peripheral or pulmonary, show similar histologic patterns ranging from normal vessels to obliterative arteriolosclerosis. However, in the great majority of cases reported in the literature as primary pulmonary hypertension, significant vascular changes have been demonstrated in the small arteries of the pulmonary circuit. Dresdale and associates feel that such sclerotic changes, when present, are secondary to the prolonged pulmonary hypertension. However, Owen and his associates [2] point out that multiple silent pulmonary emboli may arise from the peripheral veins or occasionally from the right chambers of the heart and may lead to marked right ventricular hypertrophy with histologic changes in the small pulmonary arteries which are indistinguishable from those described in so-called primary pulmonary hypertension. The possibility also exists that pulmonary hypertension may develop as the result of thrombosis in situ in the pulmonary vascular tree. The question may therefore be legitimately raised concerning the existence of primary pulmonary hypertension as an entity. The divergence of opinion which exists is well illustrated by the varying opinions recently expressed by the following outstanding authorities in personal communications to the authors. Cournand wrote, "I cannot deny that the syndrome might exist in very rare instances. It is essential, therefore, to maintain a critical viewpoint concerning this subject and to exhaust all mechanical factors before invoking derangement of a vasomotor control which appears very unlikely as a source of hypertension."[3] Sprague is even more dubious, stating, "I do not believe we recognize a condition 'essential pulmonary hypertension' except on the basis of structural changes in the finer vessels of the lungs."[4] Dexter, however, stated, "I believe that there is indeed a disease which ought to be called 'essential pulmonary hypertension,' that is to say hypertension not due to any apparent cause other than an increased resistance to blood flow through the small vessels of the lung for which there is no evident cause."[5] Bing remarked, "I think cases of essential pulmonary hypertension should be presented as a rather new entity. We had one patient like this with autopsy findings, a child 12 years old who was catheterized."[6] In a recent report Schafer [7] and his associates describe in detail three cases of what they believe represent essential pulmonary hypertension.

In our opinion the existence of essential pulmonary hypertension as an entity can only be accepted if the following three criteria are met:

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1. The demonstration of right ventricular hypertrophy in the absence of any other cardiac abnormality.

2. The demonstration, by cardiac catheterization, of an elevated pulmonary artery pressure and of a normal pulmonary wedge pressure.

3. Absence at necropsy of occlusive lesions in the pulmonary vascular tree unless such lesions are so sparse that they could not possibly account for the hypertension in this circuit.

The finding of cases which strictly meet these criteria would establish the existence of primary pulmonary hypertension. No information would, however, be forthcoming with regard to its incidence, since it is quite likely that vascular changes could occur secondary to pulmonary hypertension, thus nullifying the third criterion.

It is the purpose of this paper to review briefly the physiology of the pulmonary circulation in order to determine whether increased tonus in the pulmonary circuit is theoretically possible, to review the reported cases of primary pulmonary hypertension in the light of the above criteria, and to report one necropsied case of our own which meets these criteria almost in their entirety.

Physiology of the Pulmonary Circulation

The present status of our knowledge regarding the physiology of the pulmonary circulation has been reviewed in several recent excellent articles.[8,9] We shall attempt to summarize here only some of the more pertinent observations.

I. Neural Regulation.—There is abundant evidence that the small pulmonary arteries have muscular walls and are provided with nerve endings[10,11] and that there are pressoreceptors on both the arterial and the venous side of the pulmonary circuit.[12-14] There is also ample evidence[8] that the pressure changes are monitored locally in the pulmonary bed and that after central transmission reflex adjustments are brought about in the pulmonary and systemic circulations.[15,16]

Autonomic regulation of the pulmonary circuit has often been held to be insignificant.[17,18] However, the demonstration that autonomic blocking agents, such as tetraethylammonium chloride (TEAC), reduce the pulmonary artery pressure and pulmonary vascular resistance in certain patients with pulmonary hypertension suggests that at least one component of the increased vascular resistance is mediated through the autonomic nervous system.[19,20]

II. Respiratory Gases.—There is ample evidence from animal studies[18,21,22] and from catheterization data[23-25] that hypoxia causes a rise in pulmonary artery pressure. This response is not prevented by vagotomy or stellate ganglionectomy[21] but fails to occur in dogs previously subjected to transthoracic sympathectomy.[22] Calculation of the pulmonary vascular resistance from wedge pressure measurements points to pulmonary arteriolar constriction as the mechanism probably responsible for the pulmonary hypertension.[24,25] However, other investigators, working with dogs, demonstrated an increased cardiac output with hypoxia and suggested this as the mechanism for the increased pulmonary artery pressure.[26,27] Perhaps the degree of hypoxia determines whether pulmonary vasoconstriction occurs.[13]

It has been demonstrated that when the pulmonary artery pressure is elevated as the result of either cor pulmonale[24] or mitral stenosis,[29] inhalation of 100% oxygen often results in a drop in pressure, apparently due to a reduction in pulmonary vascular resistance.[20] Such changes do not occur in the normal subject.[24]

Although several groups of investigators have found that the degree of pulmonary hypertension varies with the severity of hypercapnia,[30,31] this has not been in accord with our own experience.[32] Inhalation of carbon dioxide increases pulmonary artery pressure in patients with chronic

pulmonary disease[30] but not in normal human subjects[33] or in dogs.[22]

III. Pharmacologic Agents.—Pulmonary artery pressure rises after the administration of both epinephrine and arterenol.[34] In the case of the latter drug this was demonstrated to be due to an increase in pulmonary venous pressure rather than to pulmonary arterial constriction.[35] Dihydroergotamine likewise produces an elevation of pulmonary artery pressure.[36] TEAC,[20, 36,37] pentolinium,[38] hexamethonium,[37] tolazoline (Priscoline),[1] theophylline,[37] Dibenamine (N,N-dibenzyl-β-chlorethylamine),[36] and glyceryl trinitrate (nitroglycerin)[39] have been demonstrated to reduce pulmonary artery pressure when it is pathologically elevated. TEAC produced no such change in normal subjects.[19] The ganglionic blocking agents have been considered by most investigators[12,19,36] to lower pulmonary artery pressure through vasodilatation, but Swedish workers[37] have suggested an alternate explanation that these drugs produce pooling of blood in the systemic circulation with diminution in venous return.

There are thus various mechanisms by which adjustments of pressure in the pulmonary circuit can occur. While some of these adjustments may be brought about passively as the result of alteration in the systemic circulation, there is abundant evidence that the smaller branches of the pulmonary arteries are capable of constricting or dilating as the result of a wide variety of stimuli. It is evident, therefore, that pulmonary hypertension may be brought about not only by anatomic lesions producing narrowing of the pulmonary vascular bed, but that, at least in short-term studies, physiologic mechanisms may also be involved.

Review of Reported Cases of So-called Primary Pulmonary Hypertension

The literature pertaining to this subject was searched with the realization that this condition has been reported under various titles, such as "primary pulmonary vascular sclerosis," "right ventricular hypertrophy of unknown origin," "idiopathic pulmonary hypertension," "primary proliferative pulmonary arteriolar sclerosis," "obliterative pulmonary arteriosclerosis," and "essential pulmonary hypertension."

It became readily apparent that many of the cases were reported prior to the advent of cardiac catheterization or, for various other reasons, were not studied with this procedure. Among such reports, those of McCallum,[40] Brill and Krygier,[41] Gilmour and Evans,[42] Kaump and Dry,[43] Brinton,[44] Spencer,[45] Symmers,[46] Aitchison and Richmond,[47] Owen and associates,[2] Seely,[48] Berthrong and Cochran,[49] Parmley and Jones,[50] Cross and Kobayashi,[51] Killingsworth and Gibson,[52] Norris,[53] one case of Dressler,[54] and all but one of the cases of Brenner[55] demonstrated gross or histologic changes in the pulmonary vasculature which could produce right ventricular hypertrophy from hypertension in the lesser circuit on a mechanical rather than on a functional basis.

Among cases having cardiac catheterization, those of Chapman and associates,[56] Wood,[57] Johnson and co-workers,[58] three of those of Dresdale et al.,[1] and two of those of Dressler[54] did not come to autopsy. Howarth and Lowe[59] also reported two patients in whom they state the clinical diagnosis of primary pulmonary hypertension was supported by cardiac catheterization and confirmed at necropsy, but no description of the autopsy findings are recorded. Other cases demonstrating significant pulmonary vascular changes at autopsy in which cardiac catheterization has been performed during life are those of Werkö and Eliasch,[60] Bauersfeld and co-workers,[61] Cutter and associates,[62] Inkley, Gillespie, and Funkhouser,[63] and Dexter et al.,[64] as well as two cases of Schafer and associates[7] and one case of Dresdale.[1]

The reports of the following authors are of interest in that, although the patients

were not catheterized during life to fulfill absolutely the criterion of pulmonary hypertension, there was at autopsy unexplained right ventricular hypertrophy together with probably or at least possibly insignificant pathologic changes in the pulmonary vasculature:

1. Ulrich's [65] second case was a 27-year-old woman who had had symptoms on exertion since the age of 15. She developed progressive dyspnea as well as peripheral edema, hoarseness, and occasional blood-tinged sputum. Terminally there was marked cyanosis. The red blood cell count was 5,000,000, and the hemoglobin, 108%. At necropsy the heart weighed 360 gm. The left auricle and left ventricle were normal, whereas the right auricle and right ventricle were greatly dilated and moderately hypertrophied. The pulmonary artery was dilated and larger than the aorta. The tricuspid and pulmonary valves were dilated. There was sclerotic thickening of the larger branches of the pulmonary artery and dilatation of some of the middle-sized branches. Although many sections of the lungs were examined, no evidence of sclerosis of the arterioles was demonstrated.

2. Oppenheimer's [66] second case presented at autopsy a huge pulmonary artery, together with its main branches, and a small aorta. The right ventricle was hypertrophied, while the left was described as small. There was no malformation of the heart. Grossly the lungs were normal except that the pulmonary arteries and their main branches, extending peripherally almost to the pleural surfaces, were dilated. These vessels showed some arteriosclerotic plaques, but their lumina were not compromised. Histologically, these plaques consisted of intimal thickening with lipid deposition. The pulmonary arterioles showed only slight intimal thickening, and their lumina were completely patent.

3. Raaschou and Samuelsson [67] report the case of a 59-year-old man who, in the seven years preceding death, had anginoid pain in the precordial region, severe cyanosis, dyspnea (without pulmonary congestion), and edema of the lower extremities. The electrocardiogram showed progressively increasing right axis deviation. He was hospitalized on five occasions and terminally had icterus, polycythemia, severe hepatomegaly, edema, and pronounced cyanosis. Terminally he developed empyema. At autopsy the heart weighed 745 gm. The right ventricle measured 10-14 mm. There was no congenital abnormality, and the valves were normal except that the pulmonic valve was dilated to a circumference of 100 mm. There was slight atheromatosis but no thrombosis of the branches of the pulmonary artery. These vessels were dilated. There were no microscopic changes in the pulmonary arterioles. There was no sign of lung or pleural disease except for empyema of recent onset.

4. McKeown [68] found 4 cases out of 6770 necropsies in which there was idiopathic right ventricular hypertrophy without any demonstrable lesion in the pulmonary vasculature or parenchyma. No details of the clinical or autopsy data of these cases were included in the report.

5. East [69] reported three autopsied cases of unexplained right ventricular hypertrophy. The lungs of the first case, however, were not studied microscopically. The second patient was a 24-year-old woman who had had several attacks of right ventricular failure in the previous six years. She presented with signs of ascites, hepatomegaly, slight peripheral edema, and venous distention, but no cyanosis. There was clinical evidence of right ventricular hypertrophy, an accentuated pulmonic second sound, and a slight systolic murmur localized at the apex. She improved under treatment, but on the day before contemplated discharge from the hospital she collapsed, became cyanotic, was noted to have auricular fibrillation transiently, and died a few hours later. At necropsy the heart weighed 425 gm. When the ventricles were separately dissected, the right weighed 210 gm. and the left 131 gm. The left ventricle was described as normal, whereas the right

presented a massive wall with thickened trabeculae. The tricuspid valve was not diseased but was greatly dilated. The pulmonary artery measured 90 mm. just above the cusps and showed several small atheromatous patches. The mitral valve showed slight thickening of the posterior cusp but was otherwise normal, as were the remaining valves. Microscopic sections of the heart showed hypertrophy of the fibers of the right ventricle. The muscle coats of the pulmonary arteries were perhaps a little hypertrophied, but there was no proliferation of the intima or any obliteration of the lumen of any of the pulmonary vessels.

East's third case was a 31-year-old woman who first noted dyspnea some six months previously while playing tennis. Five weeks before admission she had a miscarriage, after which there was a pronounced increase in dyspnea. Edema of the feet appeared only a few days before admission. On physical examination, the heart demonstrated a right ventricular thrust with an accentuated closure of the pulmonic valve. There were no murmurs, but gallop rhythm was present. The blood pressure was unobtainable, and the extremities were cold and blue. Cyanosis increased, as did venous distention. Drowsiness increased to coma, and she died on the second day after admission. At necropsy the heart weighed 372 gm., the separated right ventricle weighing 180 gm. and the separated left ventricle weighing 112 gm. The tricuspid valve was dilated, as was the pulmonary artery (circumference 85 mm.), which showed small flecks of atheroma. There were otherwise no gross findings in the heart or pulmonary artery tree. Microscopically the fibers of the right ventricle were hypertrophied. The lungs showed no disease except as described as follows: "The muscular coats of the smaller arteries were perhaps a little thickened. Here and there a few of the smallest arterioles were partly obliterated by proliferation of the intima, but this was not a common finding. A few of the larger arterioles showed crescentic patches of intimal proliferation with some vacuolar degeneration." In his discussion East stated that "the pulmonary arterioles showed some degree of obliteration here and there, but it is hard to believe this was extensive enough to affect the right ventricle."

6. DeNavasquez, Forbes, and Holling [70] reported three autopsied cases, sections of the lungs being taken at intervals of 1 cm. from the hilum to the periphery. The first was a 55-year-old man, admitted to the hospital with dyspnea, cough, anorexia, edema, and ascites of 12 days' duration. He had had four similar attacks which had improved with rest in bed. Physical examination disclosed marked dyspnea, venous distention with pulsation of the neck veins, free abdominal fluid, marked edema of the ankles, blood pressure of 120/72 mm. of Hg, and a regular pulse of 120. He became comatose and died on the night of admission. At necropsy the heart was greatly enlarged (650 gm.), the myocardium of the right ventricle (165 gm.) being described as three or four times its normal thickness and the left ventricle (140 gm.) as being normal. The tricuspid and pulmonic valves were very dilated but otherwise normal. The mitral and aortic valves were normal except for slight atheroma. There were no congenital abnormalities. The pulmonary artery was dilated and displayed slight atheroma in streaks. The pulmonary arterial tree was dissected as far as the arteries measuring 2 mm. in diameter, but no abnormality was found. Microscopically the alveoli of the lungs were of normal size and air-containing, the alveolar walls at the bases being irregularly thickened by capillary congestion. There was no acute or chronic inflammation of the lungs. "The arteries of 1 cm. to 2 mm. in external diameter, showed crescentic thickening of the intima by varying degrees of athermoma; though the elastic tissue of the media was conspicuous, it was impossible to be certain that it was increased. The arteries of less than 2 mm. in diameter were devoid of intimal changes and the media appeared normal."

Their second case was a 30-year-old man who had had dyspnea for a year, four attacks of unconsciousness and frequent episodes of dizziness during this interval, and cough for one month. Physical examination revealed a blood pressure of 125/95 and an apical pulse of 80-90. A systolic murmur was present at the apex. The lungs were clear. The liver was palpable and tender. There was cyanosis but no edema. Death occurred three days after admission. At necropsy the heart weighed 530 gm., the right and left ventricles, excluding the septum, weighing 153 gm. and 133 gm., respectively. All of the valves were normal except that the tricuspid and pulmonic were very dilated. The heart was otherwise normal grossly and histologically. The pulmonary artery and its branches extending to the periphery of the lungs were dilated and showed atheroma in streaks and plaques. Histologically the alveolar spaces of the lungs were air-containing and devoid of any abnormality. "The larger branches of the pulmonary artery from 1 cm. to 3 mm. in external diameter showed irregular thickening of the intima by atheroma, but the media appeared normal. The arteries of lesser caliber than 3 mm. were devoid of intimal changes, while the media appeared thickened by hypertrophy, being 20% of the external diameter; but since the media in arteries of this size varies from 6 to 32% of the diameter with a mean of 16% (Brenner) it is doubtful whether 20% is indicative of medial hypertrophy."

The third case of DeNavasquez et al. was a 49-year-old man, who had noted dyspnea for three months after an attack of influenza. He also noted constant precordial pain, uninfluenced by exertion but aggravated by deep breathing. He had had a chronic productive cough for years. Physical examination disclosed dyspnea (respiratory rate 30-50 per minute) orthopnea, cyanosis, and clubbed fingers and toes. The venous pressure was not increased, and there was no edema. The blood pressure was 104/74. The heart was clinically and radiologically slightly enlarged, but presented no other abnormality. The chest showed rhonchi at the bases and a diminution in breath sounds. The liver was just palpable and somewhat tender. The hemoglobin was 125%, and the red cells numbered 6,600,000. The patient improved sufficiently in two months to return to work as a leather dresser. During the following two years the patient was readmitted twice to the hospital with essentially the same findings except that later chest roentgenograms showed an increased transverse diameter of the heart and prominence of the pulmonary artery. All electrocardiograms showed marked right axis deviation. Circulation times with dehydrocholic acid (Decholin) and with paraldehyde were normal. The patient died approximately 28 months after the onset of symptoms. At necropsy the chest was described as barrel-shaped with a wide intercostal angle. The heart weighed 630 gm., and the right and left ventricles, excluding the septum, 162 and 129 gm., respectively. The tricuspid and pulmonic valves were dilated, but all valves were structurally normal, apart from fatty atheroma of the anterior cusp of the mitral. There were no developmental abnormalities. The pulmonary artery was uniformly dilated as far as the first division. The second branches showed patches of atheroma. The remaining branches down to 2 to 4 mm. diameter appeared normal. Histologically the capillaries throughout the lungs were engorged. No abnormality could be detected in the arteries of 1 cm. to 2 mm. diameter. In some sections the smaller arteries were dilated; in others they appeared constricted. The alveoli were air-containing and devoid of cells, and there was no evidence of inflammatory disease. The authors did not feel that this patient had significant emphysema at autopsy.

7. Rosenbaum's [71] first case was a 14-year-old girl who suffered from dyspnea, hemoptysis, and dizziness and who demonstrated a moderately loud blowing systolic murmur, a short faint early diastolic murmur along the left sternal border,

slight polycythemia (hemoglobin 16.6 gm.), but cyanosis only terminally. At autopsy, the heart weighed 344 gm., with an expected average of 157 gm. for this age. The right ventricular wall was 7 mm. in thickness, while the left ventricular wall measured only 8 mm. The right auricle was moderately dilated. All valve leaflets were normal, there was no cardiac malformation, and the coronary arteries were normal. The main pulmonary artery was slightly dilated, and the left and right pulmonary arteries down to their smallest branches appeared to be dilated. There was early infarction of the lower two-thirds of the left lower lobe, apparently "resulting from a rider's embolus extending into the main arterial branch to the lower lobe and straddling into a small radicle from this branch."

The report did not describe the microscopic sections of the small branches of the pulmonary arteries. For this reason we are not willing to accept this case as unequivocally fulfilling the third criterion which we have set up.

8. Brenner[55] reported the case of a 27-year-old woman who was first seen in 1924 and who died in 1929. Autopsy showed marked right ventricular hypertrophy (11 mm. thickness, compared with 13 mm. for the left ventricle). There were no other cardiac abnormalities. The pulmonary artery was greatly dilated (circumference of 13 cm.). The branches were also dilated without constriction or obstruction. There were many small scattered atheromatous patches in the stem and main branches. Microscopically the stem of the pulmonary artery showed diffuse intimal thickening, with round and oval cells and clumps of fat-containing foam cells. In the depths of the intima there was much elastic tissue and longitudinal muscle. The media and adventitia appeared normal. Many large intrapulmonary arteries showed similar changes. Others showed only slight intimal thickening, and others were normal. Many small muscular arteries were normal, but some showed fibrous intimal thickening, slight or marked, with narrowing of the lumen. Fibrous tissue was sometimes dense and hyaline and sometimes loose and cellular. In some, the intima contained capillary lumina. A few arteries were blocked by dense fibrous tissue, with recanalization by small capillaries. Venules and small veins were greatly dilated. No large veins appeared in the sections. The lung tissue showed great congestion and acute bronchopneumonia but no chronic inflammatory or fibrotic lesions. In his comment on this case Brenner stated that the changes were those of ordinary atherosclerosis and were no greater than in the many cases in which heart failure was not present and the right ventricle was of normal thickness. Whether or not these pathologic changes in the pulmonary circuit were sufficient to produce pulmonary hypertension leading to the right ventricular hypertrophy seems to us to be a moot question, and we are, therefore, reluctant to accept this case as meeting our third criterion.

To our knowledge there have been only two cases in which cardiac catheterization demonstrated elevation of the pulmonary artery pressure and autopsy failed to show occlusive lesions in the pulmonary vascular tree which might account for this hypertension. One is Whittenberg's case[72] (cited by Dresdale et al.,[1]) the description of which was not available to us. The other is Soothill's patient,[73] a 22-year-old man who had had dyspnea of sudden onset nine months before admission to the hospital. One month after the initial symptom he noted blurred vision and lost consciousness for five minutes following exertion. Edema developed two months and orthopnea, hoarseness and cyanosis three days before admission. Alteration in the shape of the nail beds had been noted in the previous six months. Significant physical findings included a blood pressure of 120/90, a systolic murmur and a mid-diastolic third sound at the apex, and a greatly accentuated and split pulmonic second sound. Laryngoscopy revealed paralysis of the left vocal cord. The hemoglobin was 100%, and the red blood cells numbered 5,000,000. The

electrocardiogram demonstrated clear-cut evidence of right ventricular hypertrophy. Pressures measured by means of cardiac catheterization were as follows: right auricle, 26/12; right ventricle, 154-106/17; pulmonary artery, 128/83. The oxygen values showed no evidence of a shunt. The cardiac output was 1.3 liters per minute per square meter of body surface.

The patient died five months after admission. There was a single giant bulla at the apex of the right lung. The heart weighed 500 gm., with a right ventricle of 7 mm. and a left ventricle of 12 mm. There were atheromata of the main branches of the pulmonary artery but no evidence of occlusion of these or of the smaller arteries or "arterioles." However, the author states that "unfortunately the preservation had not penetrated the wall so histological examination was not ideal."

Report of a Case*

A 17-year-old white boy was admitted to the Cincinnati General Hospital on Jan. 20, 1949. His complaint at that time was shortness of breath and abdominal distention.

Past Illness.—In 1944, five years before admission to the hospital his illness began insidiously. The first symptoms followed a blow across the chest by a baseball bat. This occurred in 1944, and merely dazed him for a few seconds. A short time afterward, intermittent abdominal swelling and progressively severe exertional dyspnea were noticed. On three occasions he fainted during severe exertion. His mother had noticed fleeting cyanosis of the hands for six months. There was no orthopnea, chest pain, or hemoptysis. A mild nonproductive cough had been present for years.

Physical Examination.—T., 98.2 F; P., 60; R., 28; B. P., 110/60 (supine); weight, 137 lb. The patient lay comfortably flat in bed. There was marked abdominal enlargement. There was moderate cyanosis of the hands and feet, but none of the lips and tongue. The neck veins were distended. Dullness and diminished breath sounds were present over the right lower chest, and asthmatic sounds were heard throughout both lung fields. The cardiac apical impulse was located 2 cm. to the left of the midclavicular line and was discrete and forceful. Cardiac dullness extended 3 cm. to the right of the sternum. A loud systolic murmur was present over the apex. The pulmonic second sound was greater than the aortic. The abdomen was tense with fluid, yet the liver could be palpated 10 cm. below the right costal margin. It was smooth and did not pulsate. A moderate degree of pedal edema was present.

Laboratory Data.—Hgb., 15.5 gm.; RBC, 5,800,000; WBC, 7250, with 69% granulocytes, 29% lymphocytes, and 2% monocytes. Urinalysis was normal. The blood urea nitrogen was 6.8 mg. The Kahn test was negative; serum protein, 6.5 gm. per 100 cc.; thymol turbidity, 1.5 units; cephalin flocculation, negative in 24 hours; serum bilirubin, 0.5 mg. per 100 cc. direct, 2.0 mg. total. The electrocardiograms showed regular rhythm with incomplete right bundle-branch block. Venous pressure was 450 mm. of water. Circulation time (arm to tongue) was 44 seconds. Vital capacity was 46% of normal.

Cardiac Fluoroscopy.—"The transverse diameter is greatly enlarged to both right and left. No pulsations are seen along the lower right heart border, and only slightly on the left and elsewhere including the aorta. The aortic knob appears very small and no aortic imprint is demonstrated in any view. The esophagus is displaced posteriorly in the right oblique in a diffuse manner. The pulmonary arc segment is not particularly prominent. In the left oblique the enlargement appears to be chiefly anterior. The superior vena cava is slightly prominent in the AP view and congestive changes of a mild degree are seen in the lungs. The diaphragms move poorly."

Angiocardiography.—"The veins of the right shoulder and the superior vena cava are clearly outlined and show no evidence of obstruction or other abnormality. An accumulation of dye of rounded contour is located in the region of the superior vena cava just above the heart shadow, and this persists throughout the entire examination. The right auricle, right ventricle, and left pulmonary artery are clearly demonstrated. The right auricle and ventricle are rather markedly enlarged, and occupy most of the cardiac shadow in the AP view, in which this examination is performed. The left side of the heart is not clearly visualized at any time, although there is probably opacification of the left auricle in the last film which is taken about 30 seconds after the injection of dye. The left ventricle and the aortic shadow are never visualized."

Cardiac catheterization was performed on Jan. 25, 1949, with the following results:

Right atrial mean pressure, 28 mm. Hg.
Right ventricle pressure, 99/29 mm. Hg.
Pulmonary artery pressure, 98/59 mm. Hg.
Oxygen content
Superior vena cava, 10.0 vol.%

*A brief description of this case has been previously reported.[74]

Right atrium, 9.6 vol.%
Right ventricle, 8.3 vol.%
Pulmonary artery, 9.6 vol.%
Femoral artery, 19.2 vol.%
(Capacity), 19.9 vol.%
Arterial oxygen saturation, 97%

Course.—Salt restriction was instituted, and 15 lb. of weight was lost. Following discharge, Feb. 4, 1949, fluid retention increased despite vigorous mercurial treatment and a trial of digitalization. Abdominal paracentesis was necessary for relief on April 25. By May 12 the patient had developed orthopnea and nocturnal coughing. The systolic apical murmur was much less distinct. Fluoroscopy revealed findings as before.

Diuresis was fairly satisfactory with daily administration of meralluride (Mercuhydrin), but on July 11 a right inguinal hernia appeared which contained fluid. Numerous paracenteses were performed. In October, 1949, the patient noted an increase in exertional dyspnea, orthopnea and coughing, and diuresis became less satisfactory. On Jan. 27, 1950, an exploratory thoracotomy was performed because of the opinion held by some that the patient had chronic constrictive pericarditis. At operation, enlargement of the right auricle and right ventricle were noted. There was questionable enlargement of the left ventricle. No evidence of pericardial constriction was found, and the chest was closed. Postoperatively the patient did poorly, and he died two days later.

Autopsy Findings.—A complete postmortem examination was carried out three hours after death. The sutured thoracotomy wound in the anterior midline of the chest measured 24 cm. Numerous puncture wounds indicated the sites of venous infusions and abdominal paracenteses. There was mild scrotal edema. A recent small extravasation of blood was found in the anterior mediastinal interstices. The right pleural cavity contained 200 cc. of serosanguinous fluid, the left was clear.

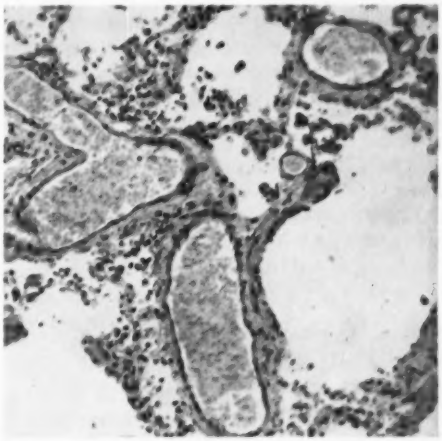
The right lung weighed 700 gm., the left, 475 gm. Save for complete atelectasis of the right lower lobe, the lung substance was expanded and crepitant and did not collapse completely with removal of the chest plate. On serial section there was dependent congestion and a small 1.0 cm. hemorrhagic infarct abutting upon the posteroinferior margin of the left upper lobe. The bronchial tree was clear, and there were no other grossly perceptible areas of consolidation. A detailed scrutiny of the pulmonary vascular system revealed no thrombi or evidences of arteriovenous shunt. There was mild soft atheroma formation (2-3 mm.) in the major pulmonary arteries, and the pulmonary trunk was slightly dilated.

Pericardium: A 14 cm. midline vertical incision in the anterior wall of the sac was closed with interrupted black nonabsorbable (silk) surgical sutures. A flat sheet-like film of absorbable gelatin sponge (Gelfoam) overlay the anterior surface of the heart. There was slight serosal dulling elsewhere but no free fluid or adhesions.

Heart: The heart weighed 475 gm. and measured 17.0 cm. in a transverse line. The chest diameter was 31 cm. There was pronounced dilatation of the right atrium and ventricle. On section, the right ventricle, though dilated, measured 5 to 8 mm. in thickness, and the left ventricle, 16 mm. The myocardium was firm, homogenous, and grossly unremarkable. The cavities contained neither antemortem thrombi nor valvular vegetations. The valves themselves were thin, filmy, and of normal texture. They measured, respectively, as follows: the tricuspid, 140 mm.; the pulmonary, 80 mm.; the mitral, 115 mm., and the aortic, 55 mm. in circumference. Small foci of subendocardial fibrosis were noted in the posterior wall of the right atrium. The endocardium was otherwise unremarkable, but there was marked dilatation of the right ventricle and atrium, with cupping of the outflow tract. Despite the dilatation, the trabeculae carneae of the right heart were unduly prominent and hypertrophied. The coronary arteries and the major vessels exhibited no anomaly, significant abnormality, shunt, or occlusion. There was considerable dilatation of the vena cavae and the innominate veins.

The liver was strikingly enlarged, weighing 2810 gm. It was the seat of profound congestion, with a deep purplish hue and marked prominence of centrolobular markings. The remainder of the examination, including that of the head and brain, was unrevealing.

Fig. 1.—Pulmonary arterioles without significant abnormality. The vessels are thin-walled and evidently distensible.



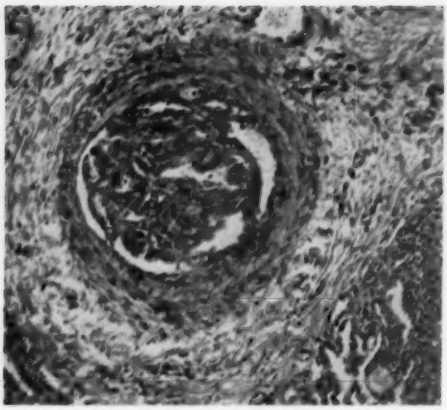


Fig. 2.—An organized and recanalized thrombus in a small peripherally situated arteriole within a pulmonary septum.

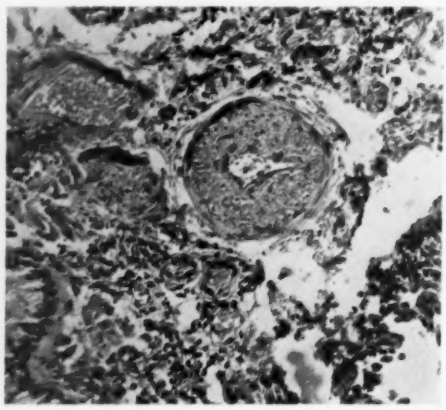


Fig. 3.—A pulmonary arteriole exhibiting marked medial hypertrophy with narrowing of the lumen.

Microscopic studies revealed relatively little abnormality. The major viscera, including the myocardium, were normal. The liver exhibited severe centrolobular pooling of blood, disruption of parenchymal cells, and early translobular fibrosis, indicating cardiac cirrhosis of mild degree.

The lung was intensively investigated. Eighteen sections were procured from different portions of all five lobes. In many of these connective and elastic tissue stains were prepared in addition to the conventional hematoxylin and eosin stains. The sections revealed the majority of the arterioles to be entirely normal (Fig. 1). There were foci of recent atelectasis, early lobular pneumonia, spotty intra-alveolar hemorrhage, and a single small sharply outlined acute infarct. The alveolar capillaries were congested, but the septa exhibited no fibrosis, and evidences of pulmonary fibrosis, emphysema, and bronchiectasis were lacking. Detailed scrutiny brought out, by actual count, seven thrombotic occlusions of small pulmonary twigs, none exceeding 1.0 mm. in diameter (Fig. 2). These had the appearance of organizing emboli but were comparatively recent. In addition, there was encountered in various sections a total of 10 small arteries of like size which were the seat of mural muscular hypertrophy (Fig. 3). These were sparse, occurring among hundreds of such vessels, and by no means served to clarify the mechanism of this patient's disease.

Comment

Hypertension in the pulmonary circuit can be classified as primary and secondary.[75] Certainly most cases fall into the category of secondary pulmonary hypertension. The usual causes may be listed as follows[75]: (1) Congenital heart disease with large left-to-right shunts (atrial septal defect, ventricular septal defect, anomalous pulmonary venous return, patent ductus arteriosus); (2) lesions of the left side of the heart (mitral stenosis, left ventricular failure); (3) anoxia (pulmonary emphysema); (4) diffuse pulmonary vascular disease (pulmonary fibrosis, multiple pulmonary emboli, thrombosis of pulmonary arteries).

There remain the relatively rare cases of so-called primary or essential pulmonary hypertension. As may be surmised from the review of the literature, there is considerable controversy as to just what constitutes this entity.

It would appear that unless the patient has undergone cardiac catheterization the diagnosis of pulmonary hypertension cannot be absolutely established. The demonstration of isolated right ventricular hypertrophy is presumptive but not conclusive evidence of such hypertension. To establish unequivocally that the pulmonary hypertension is primary also requires that few or no occlusive lesions of the pulmonary arterial tree be demonstrated at autopsy. This stipulation sharply narrows the number of reported cases that satisfy all these criteria.

Within recent years direct measurements of pressures in the lesser circulation have revealed a number of instances of pulmonary hypertension in which the usual causes of such elevated pressures have been eliminated by careful clinical and radiologic studies.[56-58] However, recent reports [2] that multiple peripheral pulmonary emboli may silently produce myriads of tiny obstructive lesions in small branches of the pulmonary arteries without clinical or x-ray evidence of their existence has cast suspicion upon all such cases which have not had postmortem examination. In a number of cases published as examples of essential pulmonary hypertension in which marked elevation of intrapulmonary vascular pressure was demonstrated by the cardiac catheter and the tissues later examined at necropsy, the photomicrographs or description of the pulmonary histopathology clearly demonstrated the presence of multiple organized emboli or thrombi in the peripheral branches of the pulmonary arteries. Until recently the authors of these articles have either ignored the presence of these lesions or have ascribed their presence to increased intrapulmonary pressure. The opinion of the majority at the present time attributes the elevation of pulmonary vascular pressure to the obstruction of numerous finer arterial vessels by widespread embolization, often months or years before the development of right ventricular failure. Support for this belief is afforded by the experimental production of pulmonary hypertension in animals by the injection of Lycopodium spores into the veins of dogs [76,77] and of fibrin clots into the veins of rabbits.[78] Nevertheless, it would appear likely that occasionally thrombi may form in situ in small atherosclerotic branches of the pulmonary artery as the result of pulmonary hypertension.

Thus to make a firm diagnosis of primary pulmonary hypertension it would seem necessary to demonstrate the existence of pulmonary hypertension by cardiac catheterization and to eliminate all pathological lesions known to cause increased intrapulmonary pressure by autopsy with multiple sections from the lobes of the lung and detailed examination of the heart. The case that we have presented seems to us to satisfy these criteria, since detailed pathologic examination failed to reveal structural alteration adequate to explain either the marked right ventricular hypertrophy or the pulmonary hypertension demonstrated during life by catheterization. During the latter procedure a pulmonary capillary or wedge pressure was, unfortunately, not obtained. Demonstration of a normal wedge pressure would have been desirable to aid in eliminating left ventricular failure and mitral valve abnormality as significant factors in the pathogenesis of the pulmonary hypertension. However, the autopsy demonstrated no evidence of mitral stenosis, and much greater enlargement of the left ventricle would have been expected if either mitral insufficiency or chronic left ventricular failure were playing significant roles.

There are various mechanisms by which adjustments of pressure in the pulmonary circuit can occur. While some of these adjustments may be brought about passively as the result of alterations in the systemic circulation, there is abundant evidence that the smaller branches of the pulmonary arteries are capable of constricting or dilating with a wide variety of stimuli. These include the effect of drugs such as arterenol, epinephrine, and dihydroergotamine, which increase pulmonary artery pressure, and TEAC, Dibenamine, tolazoline, and theophylline, which reduce pulmonary artery pressure. Of even more clinical interest is the demonstration that hypoxia elevates pulmonary artery pressure. It is evident, therefore, that pulmonary hypertension theoretically may be brought about not only by anatomic lesions, producing narrowing of the pulmonary vascular bed, but that, at least in short-term studies, physiologic mechanisms may be involved. The exact role of these factors in the production of sustained essential pulmonary hypertension is not clear at this time.

Summary and Conclusions

A review of the literature of primary pulmonary hypertension and our own experience with one case reported here suggests that such an entity exists, although it may be exceedingly rare. The majority of reported cases of pulmonary hypertentension demonstrated by cardiac catheterization have not had postmortem study. Many cases which have come to autopsy have shown, on histological examination, widespread occlusive lesions in the pulmonary vascular tree. However, a small number of cases well studied from the clinical and pathological point of view show no anatomic explanation for the pulmonary hypertension or its anatomic counterpart, right ventricular hypertrophy. Until further knowledge affords an explanation, such patients may appropriately be regarded as having primary or essential pulmonary hypertension, analogous to systemic hypertension of unknown etiology.

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Addendum

Since this paper was submitted for publication, four other articles dealing with the subject of essential pulmonary hypertension have appeared.[79-82]

In the 10 cases studied by Shepherd et al.[79] there were localized obstructions in the pulmonary vasculature in all three which came to autopsy.

Heath and co-workers[80] reported on four patients, three of whom were studied at autopsy. One of these cases was reported to have no obstructive lesion demonstrated in the pulmonary vessels, but no statement was made as to the extent to which serial sections were studied.

Evans and associates[81] describe 11 cases in which at necropsy 2 failed to reveal any obstruction in the pulmonary vasculature.

Chapman and co-workers[82] studied 10 cases, 4 of whom came to autopsy. They stated that frequently the lumina of the small pulmonary vessels were completely obliterated.

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Progress in Internal Medicine

Syphilis

Review of the Recent Literature

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(Concluded from page 813)

Clinical Manifestations

Much new material on clinical syphilis has been reported on during this review period. The chief interest, however, has centered on the later aspects of the disease, notably cardiovascular.

Early Syphilis.—Richter [113] analyzed the time of infection of 257 females with primary and secondary syphilis in relation to the phase of the menstrual cycle. The fewest infections were seen late in the menstrual cycle when corpus luteum hormone was at its height. The largest number of infections were seen in the early part of the cycle when follicular hormone was elevated.

Alopecia Areata Due to Syphilis.—Behrman and Wild [114] reported in detail a case of alopecia areata which they ascribed to syphilis. In our opinion, their diagnosis must be questioned, since their patient lacked all other manifestations of secondary syphilis and their report did not include any data on the response to therapy. It seems quite likely that this patient had so-called idiopathic alopecia areata and unrelated latent syphilis.

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From the University of Pennsylvania Department of Dermatology, School of Medicine (Dr. Pillsbury, Professor), and Graduate School of Medicine (Dr. Beerman, Chairman), and from the Venereal Disease Control Section, Division of Preventive Medicine, Philadelphia Department of Public Health (Dr. Lentz, Chief).

Study of Acquired Childhood Syphilis in Madras.—A study was made by Rajam, Rangiah, and Sowmini [115] of children with acquired syphilis who attended the V. D. Department, Government General Hospital, Madras, over a seven-year period. Mode of transmission was believed to be nonsexual in most of the children, and in over 68% of them the source of infection was familial. Early lesions of syphilis in children and adolescents presented a fairly constant clinical pattern characterized by infrequency of primary lesions in the form of chancres, localization of the lesions on the mucocutaneous and mucosal surfaces of the buccal and genital regions of the body, infrequency of florid cutaneous and skeletal lesions, and the general well-being of the children with acquired infection. The similarity of the disease to endemic syphilis, bejel, and njovera is pointed out. Acquired childhood treponematosis is prevalent among the urban and suburban populations of cities living under physical, social, and economic environmental conditions which favor the spread of nonvenereal treponematosis.

Reinfection and Relapse in Early Syphilis. Rajam and his associates [116] reviewed the literature on the interrelationships and differences in clinical pictures and incidence of reinfection and relapse in early symptomatic syphilis. An analysis of clinical data on 12,186 patients with early symptomatic syphilis, examined and treated at the Venereal Disease Clinic of the Government General Hospital, Madras, during the years 1951-1953, inclusive, shows that reinfection

is commoner than relapse, particularly after adequate treatment. The clinical picture of reinfection following penicillin therapy for syphilis is described and discussed. Intervals between primary infection and reinfection or relapse are compared. The incidence of relapse and reinfection following both adequate and inadequate treatment is discussed.

Late Syphilis.—Castigliano [117] presents the problem of syphilis and oral cancer in a forceful manner. His article is based on 2250 oral cancer patients treated at the American Oncologic Hospital in Philadelphia. Tertiary syphilis, usually a disease of middle age, is perhaps the commonest disease with which oral cancer is confused. Castigliano states: "Almost always when evidences of tertiary syphilis are present in the oral cavity, the patient has an associated cancer." Although pure oral syphilis is rare, it is important to recognize that syphilis is frequently found to complicate oral malignancy, particularly cancer of the tongue. Nearly 30% of the tongue cancer cases have a reactive serologic test for syphilis. This figure is about six to nine times the average incidence of syphilis in the male white population in this country. Syphilis is even more commonly associated with oral cancer in certain countries of the Orient. Thus it can be seen that it is most unwise and dangerous to think of uncomdiagnosis when confronted with a patient presenting an oral lesion and a reactive plicated tertiary syphilis as the complete STS. Tertiary syphilis can wait two or three weeks or much longer for therapy, but cancer cannot wait; these few weeks may spell the difference between success and failure. The patient suffering from suspected glossitis, gumma, leukoplakia, etc. should have immediate biopsy. Associated cancer must always be suspected at the outset in a patient with oral syphilis.

Gumma of the Hard Palate.—An excellently illustrated case of gumma of the hard palate was reported by Huebsch.[118] The patient was treated by sequestrectomy, and later platinum foil was used to give support to both the mucoperiosteal flap and the granulation tissue that formed on the bony side. The platinum foil prevented air and fluids from passing through the nasooral fistula.

Syphilis of the Trachea.—Herzog and Conrad [119] reported on a patient with a gumma of the trachea in which, following penicillin treatment, necrosis of cartilage and stenosis of the trachea resulted in sudden death due to asphyxia. The authors felt that massive penicillin treatment is dangerous in gummatous lesions of the airways and in syphilitic aortitis. The histopathologic findings are presented in detail.

Peripheral Neuritis Associated with Pulmonary Lesion in Patient with Syphilis.—Knight and Fowler [120] described a case with a lung lesion and peripheral neuritis. Evidence is produced that the patient had syphilis, and the progress of the patient under treatment suggested that the lung lesion was of syphilitic origin. The peripheral neuritis was not thought to be specific.

Bilateral Hilar Adenopathy.—Hodgson, Olsen, and Good,[121] of the Mayo Clinic, present an excellent discussion on bilateral hilar adenopathy. It is a sign of the times that in their material syphilis gets but scant attention as an important factor in the production of these enlarged nodes (Fanconi-Hegglin syndrome [84]).

Syphilis and Tuberculosis of Respiratory System.—According to Jaffe,[122] simultaneous infection of tuberculosis and syphilis in the same person is a very frequent occurrence. Both spring from similar social evils and produce similar lesions and symptoms. Syphilis may attack the larynx, as an early or late manifestation, and involve any portion. There is a catarrhal change, congestion, mucous patches, and erosion. Tertiary lesions appear late, forming gummas, which may break down and cause scarring, retraction, and deformities. Patients with syphilis who receive prompt and adequate treatment have a fairly good prognosis, but when they acquire tuberculosis, progress is slow. Clinical evidence of pulmonary syphilis is based on the therapeutic

test and on autopsy findings. In the absence of any grave symptoms, with the sputum persistently negative, the presence of syphilitic stigmas, a positive Wassermann, and a response to a therapeutic test, syphilis should be suspected.

Congenital and Acquired Syphilis of the Stomach.—Two cases of gastric syphilis are described by Mendl, Jenkins, and Hughes.[123] One of these cases was of congenital origin. Clinical features are not of much help for the recognition of gastric syphilis, since they can simulate any other gastric lesion. Achlorhydria is probably due to a rather general type of chronic interstitial atrophic gastritis, which uniformly has been found to be present to a greater or smaller degree in the advanced cases. Reactive STS is an almost constant finding in gastric syphilis. A gastric lesion in a syphilitic patient is, however, practically never gastric syphilis. Gastric syphilis is very rare in comparison to other gastric lesions. Concerning congenital syphilis of the stomach, the authors were not able to find more than 10 cases in the world literature. Response to antisyphilitic treatment is impressive.

Gastric Syphilis with Carcinoma.—Data of an interesting case of gastric syphilis with carcinoma are copied from G. K. Chakravarty in *Surgical and Medical News* (2:22 [Oct.] 1955).[124] A subtotal gastrectomy was performed on a 50-year-old woman who showed the characteristics of both gastric syphilis and gastric carcinoma, superimposed on an ulcer. Histologic examination showed infiltrating carcinomatous cells as well as perivascular infiltration by plasma cells, lymphocytes in the wall of the stomach, and new blood vessel formation.

Uterine Cancer and Syphilis.—Røjel[125] studied clinical material comprised of 1438 patients with uterine cancer treated at the Radium Centre, Copenhagen. Names of the patients were checked in the National Registries to obtain relevant data; revenue departments were checked for income information; the syphilis register was checked, as well as police files of prostitutes. In 1262 patients with cancer of cervix uteri, there were 167 (13.2%) with syphilis. In 176 with cancer of corpus uteri, there were 10 (5.6%) with syphilis. The control series of 1392 persons included 57 (4.1%) with syphilis. Controls were chosen in such a way as to make the age and social distribution as close to that of the patients as possible. Conclusions drawn from the study were as follows: It can be ruled out that the increased frequency of syphilis is due to variations in some of the social factors studied, and there is assumed the existence of a particularly potent carcinogenic factor among prostitutes—a factor which has no relation to syphilis. It is Røjel's opinion that the carcinogenic action is concerned with antisyphilitic therapy. Such arsenic compounds as arsphenamine could constitute the carcinogenic factor in the development of carcinoma of the uterine cervix, as well as of the tongue, in syphilis patients.

Cardiovascular Syphilis

The clinical as well as the therapeutic aspects of cardiovascular syphilis represent a large segment of the material of this review period. Of 1330 syphilitic patients referred for cardiovascular investigation, the majority of whom were examined before receiving antisyphilitic therapy, 202 (15%) were found to have cardiovascular syphilis by Macfarlane, et al.,[126] and 214 (16%) had other nonsyphilitic cardiovascular abnormalities. Cardiovascular syphilis was suspected in one patient who had been treated for secondary syphilis and in three whose disease was inherited. Criteria for the establishment of the diagnosis of syphilis are discussed. The great majority of syphilitic patients present undoubted serological evidence of the disease. Time alone will establish the value of the treponemal immobilization test in the remainder. Difficulties attending the diagnosis of cardiovascular syphilis are briefly mentioned. Necropsy results in 27 confirmed the

authors' diagnosis in all but one instance.

Calcification of Aorta as Aid to Diagnosis of Syphilis.—McCann and Porter [127] point out the importance of the radiological demonstration of calcification of the ascending portion of the aortic arch as an aid to the diagnosis of chronic syphilis. Of 19 cases in which this sign was present, 7 were serologically negative before therapy and 5 remained positive in spite of treatment.

Enlargement of Ventricles.—A method of determining the extent of enlargement of the individual ventricles either by fluoroscopy or by films taken in the left anterior oblique position is described by Ceballos and his colleagues.[128] A study of 115 cases, in which the findings were checked by clinical diagnosis, electrocardiography, and, in some instances, by angiocardiography, surgery, and autopsy findings, is presented. In the 15 instances of syphilitic aortic regurgitation here included, statistical data showing race, sex, age group, and measurements of the aorta, left ventricle, and right ventricle are tabulated. In 10 of the 15 instances, the left ventricle increased in size to up to 2 cm. or more larger than the right ventricle. The findings in syphilitic aortic regurgitation closely resembled the findings in the cases of hypertension here examined. Nadel [129] claims to have devised a means ("Old Age Test"), using blood pressure values, of determining the degree of atherosclerosis of the great vessels and its course under treatment. He believes that this procedure is of value in cases of cardiovascular syphilis.

Syphilitic Involvement of the Pulmonary Artery.—Two cases of syphilitic aortic aneurysm in which the pulmonary artery was involved are presented by Donnell and his group.[130] Usually, involvement of the pulmonary circulation becomes apparent when the aneurysm ruptures into the pulmonary artery. Clinically, this event is as a rule acute and disastrous, but occasionally the rupture occurs with survival and presents signs suggesting patent ductus arteriosus. In the first patient, the right main pulmonary artery was compressed, and pulmonary hypertension proximal to the compression resulted. In the second patient, the aneurysm ruptured into the pulmonary artery, producing an aortic-pulmonary fistula. Cardiac catheterization and angiocardiography established the specific abnormalities present in each case. As the prospect for surgical correction of such complications improves, the need for accurate diagnosis increases.

Antemortem Diagnosis of Syphilitic Aneurysm of Aortic Sinuses.—Report of Nine Cases: Diagnosis of syphilitic aneurysm of the aortic sinus was made during life by Merten's group [131] in only one of 19 patients between the ages of 17 and 60 years whose cases were collected from the literature. The aortic sinuses lie deep within the substance of the heart and are inaccessible to physical diagnosis. Nine additional cases of syphilitic aneurysm of the aortic sinuses are described in one woman and eight men between the ages of 45 and 64 years in whom the diagnosis was established during life by angiocardiography. The findings in the 9 patients were compared with those in the 19 in whom the diagnosis was made at autopsy. Two groups were recognized. Aneurysm of the aortic sinuses was associated with fusiform dilatation (aortitis) of the ascending aorta in six patients, and localized aortic sinus aneurysms were observed in three. Unlike congenital aneurysms of the sinus of Valsalva, syphilitic aneurysms may be huge and may occasionally rupture outside the heart. Aortic regurgitation was present in eight of the patients; it is an outstanding feature of aneurysm of the aortic sinuses. Next in importance is heart failure, which often may be intractable. Rupture of an aneurysm with creation of an aorticocardiac shunt is characterized by the presence of harsh machinery-like murmur associated with overloading of the chambers at the right side of the heart and the pulmonary arterial system. Rupture of the aortic sinus aneurysm occurred in 11 of the 19 patients; in 8 of the 11 the aneurysm ruptured into

the lesser circulation, and this rupture was not always immediately fatal, while rupture outside the heart always caused sudden death. Rupture did not occur in any of the authors' nine patients. The usual electrocardiographic findings of unperforated syphilitic aortic sinus aneurysm are left axis deviation and left ventricular hypertrophy. Roentgenographically, the presence of linear calcific deposits in the ascending aorta is good evidence of syphilitic aortitis; it was present in all but one patient. In several patients the conventional roentgenogram also revealed calcification in the intracardiac portion of the ascending aorta and often clearly outlined the dilated aortic sinuses. Angiocardiography demonstrates the aneurysms and their effects on the adjacent cardiovascular structures. The prognosis of syphilitic aneurysm of the aortic sinuses is not necessarily unfavorable. Of the nine patients, three were lost to observation, and of the six who were followed up for five years, two died and four are alive.

Aneurysms of the Aorta.—Clincopathologic Study of 369 Necropsy Cases: The data reported are based on autopsies performed in the pathology department of the University of Texas Medical Branch, at Galveston, from 1892 to 1953, according to Brindley and Stembridge.[132] During this 62-year period, 9273 autopsies were recorded, and in 369 cases one or more aneurysms of the aorta were demonstrated. The multiple lesions found in some aortas brought the total number of aneurysms studied to 412. The incidence of aortic aneurysms was about 4%. The majority were found in patients in the fifth, sixth, and seventh decades; however, aneurysms of the arch tended to occur in younger patients, whereas lesions of the abdominal aorta and multiple and dissecting aneurysms were found in older patients. Although aneurysms were most frequent in Negroes, dissecting aneurysms demonstrated an equal racial distribution, and abdominal aneurysms were more commonly found in Caucasians. Syphilis was the etiological agent in over half the cases (54%). Aneurysms were most often saccular and usually involved only one anatomic segment of the aorta. Multiple and dissecting aneurysms were present in 11% and 12% of the cases, respectively. An unexpected pathological finding was cardiac hypertrophy in over 80% of patients with a dissecting or abdominal aneurysm. The average duration of illness was 2 years for patients with syphilitic aneurysms and 27 months for those with arteriosclerotic aneurysms. Clinical signs and symptoms correlated well with the anatomic features of the aneurysms. While the immediate cause of death varied, rupture of the aneurysm was the commonest single cause, being found in 39% of the cases. A comparative study of the first 100 cases, observed from 1892 to 1928, and the last 100 cases, observed during the period from 1943 to 1953, indicated improvement in diagnostic acumen, better treatment, and a longer natural life span on the basis of the following trends: a decrease in the incidence of thoracic aortic aneurysms; an increase in aneurysms involving the abdominal aorta or both the abdominal and thoracic aorta; a decrease in syphilitic aneurysms; an increase of aortic aneurysms due to arteriosclerosis or cystic medial necrosis; an increase in the average age of patients with all types of aortic aneurysms; an increase in the age of patients with syphilitic aneurysms, and a decrease in the average age of patients with arteriosclerotic aneurysms. Danaraj [133] reported from Malaya an unusual case of aortic aneurysm, which was present as "multiple lumps" over the pericardium. Enselberg [134] noted that although aneurysm of the abdominal aorta is becoming more frequent, syphilis is becoming a relatively unimportant cause of this process.

Neurosyphilis

The clinical aspects of neurosyphilis have been given but little attention in this review period. In a review of neurosyphilis in general, based upon his experiences with this disease, Fabing [135] emphasized the capacity of neurosyphilis to lie dormant for long

periods of time. Consequently, though symptomatic cases of neurosyphilis are becoming rare, the possibility of the presence of asymptomatic neurosyphilis must not be forgotten. Case histories are included. In addition, the symptoms and treatment, with penicillin, of meningovascular syphilis are reviewed. Tabes dorsalis, paresis, and other late forms of neurosyphilis are best treated with penicillin and artificial fever, rather than with penicillin alone. The need for early diagnosis of paresis is stressed. Thomson [136] reported the results of spinal fluid examinations of 1821 patients (1570 males, 251 females) diagnosed as having latent syphilis. These patients were seen at three clinics in Hong Kong during the period Jan. 1, 1953, to Aug. 31, 1954. For the first 8 months, the spinal fluid was tested with the standard Kahn test, and for the last 12 months of the period, with the VDRL test. Positive Kahn or VDRL results were obtained from the spinal fluid of 132 males and 11 females. No appreciable difference has been observed thus far in results of the Kahn and the VDRL tests on the spinal fluids. It is believed that the detection and treatment of these instances will appreciably reduce the future incidence of paresis and of syphilitic optic atrophy in Hong Kong.

Congenital Syphilis

Background of Congenital Syphilis.—MacFarlane, Johns, and Schofield [137] studied 254 persons with congenital syphilis from the social as well as from the medical standpoint. On admission 14% of the patients had infantile congenital syphilis; 86%, clinical manifestations of late congenital syphilis, and 20%, latent syphilis. Interstitial keratitis was present in 56% and stigmata in 40%. It was found that 9.4% of the congenital syphilitics were illegitimate, whereas only 3.8% of the noninfected members of the family were illegitimate. The patients were also assessed in relation to poverty, general health, employment, marital status, housing, conduct, and child care; but the significance of these findings could not be assessed because no comparable statistics for the community could be found. In further comparison of the congenital syphilitics with their noninfected siblings, the congenital syphilitics were engaged in less skilled work and were in a lower social order than their fathers; whereas the noninfected fell into a higher social class, often with more skilled occupations than their fathers. For the prevention of congenital syphilis, the authors recommend routine premarital serologic testing, serologic testing of every woman in every pregnancy, and serologic and radiologic investigation of every infant born of a syphilitic mother. Laird [138] examined the records of 139 cases of congenital syphilis in children under 5 years of age reported by 22 venereal disease clinics in the Manchester Regional Hospital Board area during the five-year period 1950-1954, inclusive, to determine the cause of failure to prevent congenital syphilis. It is concluded that the practice of taking a routine antenatal blood test, while instrumental in greatly reducing the incidence of fetal infection, will not by itself prevent completely the occurrence of congenital syphilis.

Intestinal Lesions in Congenital Syphilis.—Gault and Jayaraj [139] reported the case of a patient with congenital syphilis who died at birth and who showed at autopsy many ulcerations in the small bowel. The diagnosis of syphilitic intestinal ulceration was made after the discovery of numerous spirochetes in the intestinal wall in silver-stained preparations. Using this same technique (a modified Krajian's method for staining spirochetes), the authors demonstrated numerous spirochetes in the liver, spleen, and pancreas. Unfortunately, no mention is made of the mother's history, physical or serologic examination, or treatment for syphilis; likewise, data concerning the infant's serologic tests are omitted.

Mental Abnormalities in Congenital Syphilis.—Hallgren and Hollström [140] studied 500 children with congenital syphilis from a children's hospital in Stockholm.

Three hundred twenty-eight were cases of manifest congenital syphilis; one hundred seventy-two had an obscure diagnosis of congenital syphilis or were pure observation cases. This latter group was used as a control series. Most of the children with manifest congenital syphilis received antisyphilitic treatment before the age of one year. It was found that there is a higher incidence of mental deficiency, mental subnormality, and behavior disorders (psychopathy) among subjects with manifest congenital syphilis than in the general population. However, the authors' study failed to prove statistically that there was a higher incidence of mental deficiency, mental subnormality, and behavior disorders among the children with manifest congenital syphilis than in the comparable group of control cases. Environmental and hereditary factors are of significance as causes of the above mental abnormalities in subjects with congenital syphilis. Nevertheless, it is highly probable that the syphilitic infection is in some instances the direct cause of mental deficiency.

Late Congenital Syphilitic Nerve Deafness.—Morton [141] states that late congenital syphilitic nerve deafness is in all likelihood due to labyrinthitis, although some believe it is caused by degeneration of the eighth nerve or of midbrain nuclei. Five patients treated with Roniacol (3-pyridinemethanol), the alcohol of nicotinic acid, are presented. Audiograms were not performed, and the results of treatment are far from impressive. Nevertheless, the author suggests further trial of this method of therapy.

General Therapy

The therapy of syphilis, in the Western world at least, has at last reached a satisfactory level of efficiency, with chief dependence being placed on penicillin.[142] Newer studies have indicated the value of certain adjuvants, especially cortisone.

Benzathine Penicillin in the Management of the Treponematoses.—Guthe [143] draws attention to the fact that no small proportion of the world's penicillin production is used in the management of the treponematoses and that the long-acting characteristics of procaine penicillin G in oil with 2% aluminum monostearate (PAM) have made it the penicillin preparation of choice, since the major factor in the effectiveness of penicillin is the time for which it maintains a treponemicidal level in the blood. The recent introduction of benzathine penicillin G—which, when given intramuscularly, is absorbed and eliminated about twice as slowly as PAM—represents a considerable advance in the further simplification of the management of treponemal infections. Clinical trials have shown that the same curative effect can be obtained in early treponemal infections with a single injection procedure, using a dosage of benzathine penicillin half that of PAM. Preventive treatment on epidemiological indication is an established principle in the effective management of the nonvenereal, endemic treponematoses and has been adopted in some countries in the management of venereal syphilis (and gonorrhea). The superior preventive effect of benzathine penicillin (as compared with PAM) has been demonstrated in persons exposed to contagion and in persons incubating the treponematoses. The sensitizing potential of penicillin is low, but previous experience with the antibiotic, repeated application in prolonged treatment schedules, and possibly the use of large dosages tend to increase the incidence of reactions. The number of side-reactions from penicillin is small in relation to its curative and preventive value, particularly when compared to the toxic reactions and mortality resulting from arsenotherapy. The introduction of benzathine penicillin will further limit the incidence of sensitization reactions, since lower dosages make one-session treatment schedules a practical proposition. The data available on the place of benzathine penicillin in the management of the treponematoses are still incomplete, and more time must elapse before a fuller evaluation of its advantages and disadvantages can be made. However, in some

countries, benzathine penicillin G is already replacing PAM in clinical practice in the management of syphilis (and gonorrhea). It is suggested that, when more stable presuspended preparations become available, benzathine penicillin might become the preparation of choice in the control of the nonvenereal, endemic treponematoses.

Cortisone and Syphilis.—Results of and Comments on Corticotherapy in Ninety Cases of Syphilis: Ninety patients with syphilis of various clinical forms were given cortisone, hydrocortisone, or corticotropin before a course of penicillin therapy by de Graciansky and Grupper.[144] This procedure was successful in preventing or attenuating Herxheimer's reaction. It also affected the clinical manifestation of the disease: 1. Chancres stopped oozing, became softer, and rapidly epidermized. 2. Certain features of secondary syphilis were favorably influenced, but less so as they were severer. 3. The gummas and ulcerations of tertiary syphilis were greatly benefited. 4. There was evidence to indicate that corticotherapy had an effect on the functional signs of aortic syphilis. 5. In central nervous system syphilis, pain resistant to other kinds of therapy yielded to cortisone. Local injections of hydrocortisone proved excellent in the treatment of four patients with tabetic dislocating arthropathy of the knee. 6. Symptomatic benefit was obtained in interstitial keratis of late congenital syphilis. Corticotherapy had effect also on the laboratory signs of syphilis: Treponema, reagin, amboceptor, and anomalies of the cerebrospinal fluid. The normal course of sensitivity of Treponema organisms to penicillin altered. In patients allergic to penicillin and in pregnant patients, cortisone favors a better tolerance to the antibiotic. Its value in the severe pain and visceral paroxysms of tabes, in arthropathy, and in interstitial keratitis makes cortisone an excellent adjuvant in the treatment of these forms of syphilis. Hydrocortisone appears to be the best agent to administer and is now being used routinely by the authors.

Radioisotope P^{32} for Treatment of Incurable Latent Syphilis.—Miura and his colleagues [145] gave three patients, one each with late, congenital, and early syphilis, an intravenous injection of dilute $H_3P^{32}O_4$ containing approximately 0.5 mc. of P^{32}. Three other patients, two with early and one with congenital syphilis, received 9,000,000 units of penicillin over a 15-day period in addition to the above dose of P^{32}. In the congenital syphilis patients, the dose of P^{32} was halved. In one penicillin-treated patient with early syphilis, the Wassermann reaction became negative almost immediately following administration of P^{32}; but in the other two treated patients, no change in seroreaction was noted up to four months after treatment. However, transient fluctuations in the Wassermann reaction were observed in both the treated and the untreated patients following administration of the P^{32}. This phenomenon was also observed in syphilitic rabbits. The fluctuations and the permanent change noted above are believed due to a derangement of T. pallidum in the liver and spleen by biotropism of radioactive P^{32}. Studies of this phenomenon are being continued.

Treatment of Early Syphilis

Treatment of Primary and Secondary Syphilis.—Willcox [146] has reviewed the use of penicillin in the treatment of syphilis from its introduction by Mahoney to the present and then speculates on the future. He states that not all of the world's benzathine penicillins cause pain; since pain is the big obstacle to the use of this preparation, the future will have a painless benzathine penicillin. Then treatment will consist of an epidemiological dose of 2,400,000 units of benzathine penicillin, followed by nil to four weekly injections of 1,200,000 to 2,400,000 units of this preparation. So far as today is concerned, the initial dose should be 2,400,000 units of procaine penicillin G with aluminum monostearate (PAM), which has by itself been shown to be curative in most cases of early syphilis. Thus

with a single minimum curative dose, should the patient default and not obtain the remainder of treatment, no harm will result. This so-called "epidemiological dose" has everything to recommend it. Concerning the use of arsenic and bismuth along with penicillin in a "consolidation" treatment, it is believed that there is nothing arsenic and bismuth can accomplish which penicillin cannot achieve more effectively and more safely. Penicillin has been shown to be the most effective of the antibiotics experimentally, and penicillin by injection gives better and surer results than any orally administered preparation. The other antibiotics may be reserved for patients showing sensitivity to penicillin. If asymptomatic contacts of infectious syphilitics cannot be kept under surveillance for three months, they should receive prophylactic therapy; however, if given prophylactic treatment, they should be completely followed up as though actually diagnosed syphilitic. In areas where the prevalence of syphilis is high, the regular use of the long-acting benzathine penicillin has been considered in prostitutes.

Effects of Inadequately Treated Early Syphilis.—Three case histories of syphilis relapse (all seen within a period of four weeks) were presented by Lanceley[147] to show effects of inadequate treatment and as examples of the varied clinical pictures sometimes produced by incomplete treatment of early syphilis. A common feature with all three patients was the difficulty of obtaining a history of the original infection. One patient complained of sore mouth and scrotal ulceration; one complained of sweating, lassitude, and frontal headaches, as well as fever (temperature of 101 F); the third complained of sore eyes, and upon physical examination a maculoroseolar syphilid was found on the body and limbs. All patients had been inadequately treated prior to these complaints.

Treatment of Latent and Late Syphilis

Syphilitic Cirrhosis of Liver.—Response to Penicillin and Bismuth Therapy: Doyle[148] reported a case of a man aged 36 with a diagnosis of syphilitic cirrhosis of the liver who responded well to antisyphilitic therapy with penicillin and bismuth. According to the author, there are only two other comprehensive reports[149,150] in the literature of other cases of syphilitic cirrhosis of the liver treated with penicillin.

Treatment of Cardiovascular Syphilis

In spite of the difficulties inherent in the evaluation of therapy for certain forms of syphilis of the cardiovascular system, interest in the problems of this field continues. Edeiken and Beerman[151,152] present a concise outline of the therapy of cardiovascular syphilis in which the virtues of penicillin treatment are stressed. Ganguli,[153] on the other hand, presents a brief and simple "refresher course" on cardiovascular syphilis, but unlike the American opinion, he believes that vigorous antisyphilitic treatment for this phase of syphilis is harmful and that the institution of therapy may cause a flare-up of the activity. He recommends that treatment be begun with potassium iodide or bismuth. O'Brien, Smith, and Fisherkeller,[154] in their careful study of 578 patients diagnosed before 1947 as having cardiovascular syphilis, report the following: Treatment with bismuth, alone or in combination with arsenicals, after the diagnosis of cardiovascular syphilis, had no apparent effects in prolonging life or preventing the development of further cardiovascular complications. Prognosis was poorer for males than females, and for white males in particular. Progression was more frequent among males than females and among patients with aortitis who were over 50 years of age at the time of diagnosis. Syphilitic cardiovascular disease should be searched for in younger patients than hitherto. The high incidence of co-existent involvement of the cardiovascular and central nervous system is demonstrated. The prognostic value of three factors (precordial pain, T wave and/or QRS changes, and cardiac decompensation) is suggested. The incidence of hypertension and sero-

reversal and the roentgenogram and electrocardiographic findings are presented. Uncomplicated syphilitic aortitis, if untreated or inadequately treated, shortens the expectation of life. The results obtained after five or more years' observation after penicillin treatment of a small group of patients indicate that penicillin is the drug of choice in this condition. Barnett [155] reported 44 cases of cardiovascular progression, evidenced by development of aortic regurgitation or aneurysm 1 to 20 years after adequate antisyphilitic treatment. The stage of syphilis for which therapy was given was primary in 1 case, latent in 16, benign tertiary in 7, neurosyphilis in 18, and neurosyphilis and benign tertiary in 2. Most of the patients had been under observation with routine physical examinations from the start of treatment. Almost all patients had had metal chemotherapy, but three received apparently adequate amounts of penicillin and must be considered penicillin failures. The number of injections of arsenical and heavy metals, taken together, varied from 49 to 265 (average 115). In 40 patients regularity of treatment was better than 75%. Uncomplicated aortitis was not included in the progressions. Progressions were manifested by development of aortic regurgitation in 37 patients, aneurysms in 5, and both in 2. There was no correlation between serologic and clinical outcome. Thus no reasonable amount of chemotherapy will guarantee protection against cardiovascular spyhilis, and penicillin does not always prevent progression of syphilis into serious cardiovascular disease. As the period of observation after penicillin therapy is increased, more failures are to be expected.

Outcome of Uncomplicated Syphilitic Aortitis.—Of 1330 syphilitic patients studied by Irvine, [156] 61 presented probable uncomplicated aortitis. The study indicated that there is no appreciable threat to life from uncomplicated aortitis, at least for the first 7 years after its discovery, and the only patient to die of cardiovascular syphilis survived for 14 years after his arotic lesion was discovered. The material revealed no factor of indisputable prognostic importance, but there was some evidence to show that those with symptoms at the time of diagnosis and those with greater degrees of aortic dilatation did worse than the others. No appreciable prognostic effect could be attached to age, sex, occupation, the duration of infection, the presence of an aortic systolic murmur or an accentuated second sound, the titer of the serum Wassermann reaction, or the amount of antisyphilitic treatment.

Excision of Aortic Aneurysms.—Bahnson, [157] as well as Cooley and his co-workers, [158] point out that excisional therapy for aneurysms of the aorta is now established as the method of choice. One patient who survived this operation and lived for six days, during which time all peripheral pulses were readily palpable, testifies to the feasibility of total arch resection from a technical standpoint and justifies further attempts of this kind. Adams [159] maintains that in the surgical management of aneurysms of the arch of the thoracic aorta it is technically possible to establish a shunt by-pass, utilizing a homologous thoracic aorta anastomosed proximally either to the ascending aorta or to the left subclavian artery and to resect large complicated aneurysms in this region. Vaughn and his colleagues [160] report the successful excision of an aortic aneurysm during an exploratory operation performed for a supposed paraspinal tumor.

Treatment of Neurosyphilis

Results of Five-Year Penicillin Therapy in Patients with Neurosyphilis.—Two hundred fifty-four patients with neurosyphilis associated with a positive cerebrospinal fluid were given a course of 3,000,000 or 4,800,000 units of penicillin by Orban and Lazarovits. [161] Later on courses of 6,000,000 to 9,000,000 units were given. Sixty-five patients were treated with penicillin combined with fever therapy. Of the 254 patients, 56 (22%) had the meningovascular

type of the disease, 74 (29%) were asymptomatic patients or had isolated pupillary syndromes, 60 (24%) had progressive paralysis, and 64 (25%) had tabes dorsalis. One hundred eighty-seven patients were free from complaints and had few symptoms as a result of early treatment of syphilis with large doses of arsenic and bismuth. Sixty-seven patients had lancinating pains, initial psychic disturbances, pseudoneurasthenia, ataxia, atrophy of the optic nerve, and gastric disturbances. The patients were followed for five years. Repeated courses of penicillin were given to those in whom the cerebrospinal fluid was restored to normal but later on became positive again and to those in whom the clinical aspect became worse despite improvement of cerebrospinal fluid. As a result of the penicillin therapy, 16 patients with lancinating pains became free from pain and 4 were improved. In 14 of 23 patients with psychic disturbances, the condition became stationary. Disturbances of association, capacity for concentration, and physical and psychic fatigue were improved frequently. Pseudoneurasthenia was likewise improved. Nine of fourteen patients with ataxia were improved. Of eight patients with atrophy of the optic nerve, five were improved, and in three the atrophy did not progress. Gastric disturbances could be prevented for prolonged periods. For continued success of the penicillin therapy, total doses of 6,000,000 to 12,000,000 units of the antibiotic were required for patients with meningovascular neurosyphilis, the symptomatic patients, and those with isolated pupillary syndrome, while total doses of 12,000,000 to 20,000,000 units were required for patients with tabes. Hospitalization was not required. Penicillin therapy was highly successful in patients with meningovascular syphilis, obviating the need for fever therapy. In the asymptomatic patients or in those with isolated pupillary syndrome, fever therapy was resorted to only when after the administration of at least 20,000,000 units of penicillin the cerebrospinal fluid did not improve, became worse, or became positive again after having been restored to normal. In many patients with tabes dorsalis improvement could be obtained with penicillin alone, obviating the need for fever therapy. The cerebrospinal fluid was restored to normal, and symptoms were improved. Combined treatment with penicillin and fever therapy was required for patients with advanced atrophy of the optic nerve and for some patients with progressive paralysis and tabes dorsalis.

Penicillin Treatment of Neurosyphilis.—Marceron and Ragu [162] detail five case reports of patients who had received a minimum of 6,000,000 units of penicillin for primary or secondary syphilis at some time between 1946 and 1949, who presented evidence of active neurosyphilis in 1954 or 1955. Evidence for neurosyphilis in these five cases included partially or completely positive serologic test in the spinal fluid; in all five, absence of Achilles and prepatellar reflexes; positive Romberg, and pleocytosis in the spinal fluid of 10-122 cells. The authors conclude that penicillin is relatively ineffective in preventing systemic manifestations of syphilis and that even following modern antibiotic treatment, meticulous follow-up observation of old syphilitics should be carried on. They state it is premature to believe that penicillin is completely efficacious in preventing the late manifestations of syphilis and that, on the contrary, antibiotic treatment may mask the evolution of the late manifestations. They suggest prolonged observation controlled by spinal fluid and serologic examinations as well as the treponemal immobilization test.

Chlorpromazine in Gastric Crisis.—According to a letter to the *Journal of the American Medical Association*,[163] from France, at a meeting of the Medical Society of Paris Hospitals in March, R. Moreau and his co-workers reported that in a patient with gastric crisis of tabes, which was not relieved by atropine or any other drug,

a slow perfusion with 50 mg. of chlorpromazine in 500 cc. of isotonic dextrose solution gave prompt and lasting relief. A similar result was obtained in a patient whose gastric crisis was due to plumbism and who was treated with intravenous chlorpromazine. The mechanism of this action remains obscure.

Hyperthermia Treatment of Neurosyphilis.—Methods of Evaluation and Prognostically Important Factors: Of 194 patients with neurosyphilis, 101 had been subjected by Arentsen and Welner [164] to hyperthermia treatment, 73 to combined treatment (hyperthermia simultaneously or alternating with penicillin), and 20 to penicillin. The results were made up after the first series of treatment, as well as after intensive treatment lasting for several years. After the complete treatment 58 had been given hyperthermia treatment; 119, combined treatment, and 17, penicillin treatment. The indication for retreatment was determined by making a total evaluation of the clinical, social, and humoral aspects of the patients' state. Results showed that combined treatment was not superior to hyperthermia. For all patients at an observation period of 15 months, 20% were symptom-free; 75% were symptom-free or improved, while 44% were fit for work. The cerebrospinal fluid had been normalized in 65%. After an observation of four to five years, 30% were symptom-free, 74% symptom-free and improved, while 40% were fit for work. The cerebrospinal fluid was normalized in 70%.

Treatment of Congenital Syphilis

Prevention of Congenital Syphilis by Treatment of Syphilis in Pregnancy.—Nelson and Struve [165] report their results of studying 1220 children of 423 mothers with histories of infection with syphilis. The incidence of congenital infection in children born to untreated mothers was 13.4%. In children born to inadequately treated mothers it was 5.8%. No congenital infections occurred among the children of mothers who had received at least one full course of antisyphilitic therapy, whether an arsenical, bismuth, or penicillin course. Authors state that if a pregnant woman has received at least one full course of treatment and has not since had a relapse or a reinfection there is little or no risk of the infection of her children. It does not matter how long before delivery or pregnancy this treatment is given. It is not necessary to re-treat an infected woman during subsequent pregnancies unless there has been a relapse or reinfection or there is the possibility that relapse or reinfection may have occurred. If a woman has had at least one full course of treatment and has not since had a relapse or reinfection, it does not matter that her serologic tests may be reactive, even at a high titer, so far as the outcome to the child is concerned. If, however, the mother's tests are positive, the infant's tests may also be positive up to several weeks, because of transfer of the mother's reagin to the fetal circulation, and, lacking clinical evidence of infection, it may not be possible to resolve the question of the child's infection until the child is at least 3 months of age.

Evaluation of Results of Penicillin Therapy of Congenital Syphilis in Children.—Five years' experience with 118 infants and children with congenital syphilis treated in the pediatric clinic of the Medical Academy in Poznan, Poland, prompted the following suggestions by Dembinska-Widy.[166] In premature babies and infants less than 2 months old with severe lesions, preparatory treatment should be instituted, in order to avoid a Herxheimer reaction. This treatment should consist of acetarsone (3-acetamido-4-hydroxybenzenearsonic acid), starting with half of a 0.25 gm. tablet a day and continued for two weeks. Penicillin therapy is instituted after this period. Congenital syphilis should be treated during the first year of life with two courses of penicillin therapy and one of arsenic and bismuth. No changes in the nervous system and no mental disturbance were noted by the author in the infants so treated. In the

second year of life one course of penicillin therapy is advised, with three arsenic-bismuth treatments, and in the third year, one of penicillin and four of arsenic and bismuth. If serologic resistance or serologic recurrence be encountered, as many as six courses may be used. In older children with late congenital syphilis, a too energetic treatment with penicillin or arsenic compounds may cause a Herxheimer reaction. Patients should not be discharged from observation before examination of the cerebrospinal fluid and auxiliary examinations are performed. After cessation of therapy, children should be examined periodically for three or more years.

Implantation of Bone for Saddle Nose.—In a letter to the *Journal of the American Medical Association* [167] from Australia, the advantages of implants of pieces of bone over cartilage in the reconstruction of the nose are itemized, as presented originally by Dr. H. Bruck at the Society of Physicians in Vienna, Jan. 14, 1955. This type of implant is not suitable for the syphilitic saddle nose, which is associated with a skeletal and soft tissue defect, and the latter must be overcome before a bone implant can be considered.

Herxheimer Reaction

Frequency of Jarisch-Herxheimer Reaction (J. H. R.).—Blom-Ides, Polano, and Herrmann [168] treated 394 patients with primary or secondary syphilis with the neoarsphenamine-bismuth method. Using a febrile reaction of more than 100.4 F as the criterion for the J. H. R., 23 cases of primary syphilis had a reaction, and 51 did not; 67 cases of secondary syphilis had a reaction, and 253 did not. The reaction occurred as often in primary seronegative as in primary seropositive syphilis. The frequency of such reactions was higher in primary syphilis than in secondary syphilis. No difference in frequency of J. H. R. was observed between these cases treated with neoarsphenamine and bismuth and a series of patients treated with penicillin by Farmer.[169]

Toxic Reactions to Penicillin Treatment

Much space has been devoted to the reactions to penicillin therapy in the past year. Fatal reactions are still occurring.[170,171] Examples of anaphylactoid shock with recovery were reported by Hernández and Rosa-Febles [172] and after an intracutaneous test with penicillin by de Mello and Mendez.[173]

Tuft and his co-workers,[174] at Temple University, Philadelphia, observed that of 495 patients receiving penicillin, specific positive tests occurred in 9, or 1.8%, with the incidence apparently higher in those with a history of allergic reaction to the penicillin. A positive skin test to penicillin indicative of the presence of the anaphylactic type of allergy may be highly evanescent and disappear within a short time, even within two or three months. Therefore, the shorter the interval between the occurrence of the reaction and the time of testing, the greater the likelihood of obtaining a positive skin test. A negative skin test, however, does not exclude penicillin allergy and the possibility of a reaction to a subsequent administration, especially if the patient is allergic (for example, asthmatic) and had been given penicillin previously. The most satisfactory skin test method for the detection of penicillin allergy is the intracutaneous injection of 0.02 cc. of a concentration of penicillin of 10,000 units per cubic centimeter. This may be preceded by a scratch test where exquisite sensitivity is suspected. In either instance, a control test with the penicillin diluent or vehicle should always be done at the same time to exclude a possible false-positive test. No reliance can be placed on delayed positive skin tests. Patch tests are useful only in the contact form of allergic dermatitis to penicillin but not in the anaphylactic form. Berger and Eisen [175] emphasized the shortcomings of skin testing for penicillin sensitivity and believe desensitization is not feasible.

Siegal,[176,177] however, cites much evidence to controvert this view. Several of the cases documented by him illustrated not only the recovery of tolerance to the antibiotic in full therapeutic dosage but the conversion of positive skin tests to negative.

Penicillin Reactions in a Venereal Disease Clinic Population.—Because of anaphylactoid reactions, many fatal, following use of penicillin, physicians of 24 prevention and control centers where venereal diseases are treated volunteered to cooperate in a study to investigate reactions. Smith, Cutler, and Price [178] report that during a four-month period 16,345 patients were treated; 75% received PAM, while 24% received benzathine penicillin G, and only 1% were treated with other penicillin or with more than one type of penicillin. Reactions were reported in 109 of the 16,345 patients. Urticaria was observed in 90 patients, serum sickness in 5 patients, dermatitis medicamentosa in 5, generalized pruritus in 2, dyspnea in 2, dermatophytid in 1, and erythema-multiforme-like bullous lesions requiring hospitalization in 1. Only four anaphylactoid reactions occurred. No deaths occurred. The incidence of reactions was greater in the Caucasian race than in the Negro, and greater in females than males. Incidence of reactions appeared to increase with the age of the patients up to age 50, then to decrease. The greatest incidence of reactions occurred in syphilis patients when schedules of more than a week's duration were used and also in those in which a single-session schedule was used. In addition to type of penicillin, race, sex, and age distribution, sensitization resulting from previous penicillin is thought to account for the difference in reported reaction rates in clinic and private practice. In another study [179] the injection of penicillin was found to cause some reaction in an estimated 2.5% of children, 5% of nonallergic adults, and 15% of allergic persons. When sensitivity to penicillin is suspected and another antibiotic agent cannot be substituted, it must be established whether the sensitivity is anaphylactoid in type and dangerous in degree. Brown discusses testing for penicillin sensitivity and a method for preventing penicillin reactions. No patient should be given penicillin who has not first been questioned concerning his allergic status in general and any previous reactions to penicillin in particular. A known reactor to penicillin should be instructed to carry a card stating that he is allergic to the drug. If these precautions are observed, anaphylactic reactions to penicillin can be practically eliminated.

Prevention and Treatment of Reactions to Penicillin.—It is of utmost importance to physicians using penicillin to be aware of the means recommended for the prevention and therapy of the untoward results of this treatment. This year, prophylaxis with chlorphenisamine maleate injection (100 mg. per cubic centimeter) [180]; cortisone and corticotropin (ACTH) [181]; penicillinase,[182] and antihistamines (30 minutes before an injection of penicillin) [173] were recommended. The Feinbergs have summarized the subject of allergy to penicillin in an editorial which should be read by every physician.[183] They point out that a history of allergy indicates further questioning, and if there is a suggestion of a previous immediate reaction, penicillin administration is certainly a risky venture. Under such circumstances, a skin test should be made (scratch test with about 5000 to 10,000 units per 1 cc.). If this is negative, an intradermal test should be made using 0.01 cc. of a solution containing 1000 units of crystalline penicillin per cubic centimeter. The vast majority of patients who react anaphylactically will show an immediate whealing response. If either test is positive (a wheal, erythema, and itching occurring in 5 to 15 minutes), penicillin administration is hazardous. It is felt that in a patient highly sensitive to penicillin the allergic reaction cannot be prevented by antihistamine. Epinephrine is recommended as "the first thought in case of an immediate reaction. If the reaction is moderate, 0.5 cc.

of the 1:1000 aqueous solution should be used intramuscularly, to be repeated in five minutes if needed. If the reaction is rapid or more severe, 1.0 cc. of the epinephrine solution should be injected. This should be repeated later, if necessary. If there are signs of respiratory difficulty and the reaction is severe, the epinephrine therapy should be followed by an intravenous injection of aminophylline (250 mg. or 3¾ grains in 10 cc.). Artificial respiration may be required. If the patient has survived the first 10 or 15 minutes, antihistamines may be given by injection. For more continued symptoms, such as asthma or urticaria, one may administer antihistamines orally, corticotropin, cortisone, or prednisone.

There is an obvious discrepancy between the number of fatal penicillin reactions published and those actually occurring. There are similar discrepancies in publicized reports of untoward reactions from other drugs. The physician should not have to wait to receive his warnings from published papers. The creation of a central agency where untoward reactions (toxic and allergic) could be analyzed and reported (without using the physician's name) might well result in earlier information concerning the untoward reactions to a new drug. The Committee on Research of the A. M. A. Council on Drugs is endeavoring to devise a program in which it can serve as a central reporting agency of this type."

Syphiloid Diseases

The World Health Organization has continued its efforts against the treponematoses. This is indicated by the publication of reports from various parts of the world about yaws and pinta.

Serological Study of Yaws in Java.—A report comes from the laboratory of the Treponematoses Control Project, Indonesia, by Li and Soebekti [184] of the results of the serological analyses made during the period April, 1951, to April, 1953. (The Project, which has as its aim the elimination of yaws as a public health problem from the archipelago, was established jointly by the Indonesian Government, the World Health Organization [WHO], and the United Nations Children's Fund [UNICEF]. Up to April, 1953, a total of 596,485 yaws cases had been diagnosed and treated. All sera were tested quantitatively with two cardiolipin slide tests—the VDRL slide test and the Kline slide test using LaMotte antigen —or with the Kahn test using Difco beef heart extract antigen, or with all three. A study of the mean reagin titer in untreated yaws cases showed that the percentage of seronegative reactors among clinically positive cases was low and that less seronegativity was observed among females than males. Examination of decrease in mean reagin titer after treatment by clinical group showed maximum to minimum decrease in the following sequence: early contagious, early contagious plus hyperkeratosis, ulcerative plus osteoarticular, ulcerative, hyperkeratosis, and osteoarticular lesions. The decrease tended to be greater in females than males and in patients with high than with low titer; it also varied with the age of the patient. No significant variation in decrease was noted when different PAM treatment schedules (2×1 ml., 2×2 ml., 1×4 ml.) were tested comparatively. The percentage of serological cure and improvement with all schedules was highest in persons with early yaws and in the lower age groups. Study of patients requiring retreatment at resurvey revealed no important difference in mean reagin titer between clinically cured and uncured patients suffering from palmar or plantar hyperkeratosis and ulcerative or osteoarticular lesions. Sera from clinically negative household contacts and noncontacts, with or without previous history of yaws, were tested. The results showed that among the household contacts, the number of seronegative reactors, which were not affected by age distribution, was significantly higher in the history-positive than in the history-negative group. The percentage of seropositive re-

actors was in direct proportion to the prevalence of yaws, the seropositivity rate being high in villages where the incidence was 11% to 30%.

Serological Studies of Yaws in Thailand. D'Mello and Krag,[185] in serological studies of yaws in Thailand, found the incidence of yaws in some provinces, such as Surindr, as high as 50% to 60%; in some hamlets it was as high as 70%. The lesions of yaws were grouped under six types:

Type I: (*a*) Initial lesions
(*b*) Multiple papillomata
(*c*) "Wet crab" yaws
(*d*) Other early skin lesions

Type II: Hyperkeratosis, palmar and/or plantar

Type III: Ulcerative lesions

Type IV: (*a*) Bone and joint lesions
(*b*) Bone and joint pains

Type V: Latent yaws

Type VI: Other manifestations, such as gangosa, juxta-articular nodes, depigmentation

The serological pattern in Types I and II show much similarity in that the majority of cases fall in the high titer levels. With Types IV and V there is more even distribution of cases at all titer levels. A uniform serological response is seen in the early lesions and also in hyperkeratosis cases. There are more Type IV cases among the younger groups showing high titers, while in the older groups there is a trend toward the negative side. Type V shows a regressive serology. Treatment would seem to be more effective when a single injection of 4,000,000 units of procaine penicillin in oil with aluminum monostearate or when two injections of 4,000,000 units of PAM given three days apart were used, than when two injections of 1,000,000 units of PAM were used. Decrease in titer, after being comparatively rapid in the first six months after treatment, is slow, and reversal to seronegativity at the end of a year occurred only in a small number of cases.

Mal del Pinto in Mexico. — The geographical distribution; prevalence; epidemiology; etiology; serological, clinical, and histopathological features, and treatment of pinta in Mexico, where it is estimated that there are more than half a million cases, are discussed by Marquez, Rein, and Arias.[186] It is reported that 61.6% of cases are seen in the age group of 1 to 15 years. Penicillin treatment of pinta in Mexico began in 1947. In the first Mexican mass study of the infection, 665 pinta cases in the State of Guerrero were successfully treated with a single dose of 1,200,000 units of PAM. Later, other antibiotics (oxytetracycline [Terramycin], chlortetracycline [Aureomycin], streptomycin, chloramphenicol) were also employed; although these were effective, the response was slower, and the darkfield disappearance time of treponemes from the lesions was longer than with penicillin. Recently, the use of Panbiotic—a combination of 300,000 units of potassium penicillin G, 300,000 units of procaine penicillin G, and 600,000 units of benzathine penicillin G—has been introduced. The schedule employed is a one-shot dose of 2 ml., and the results in 92 patients are reported.

Control of Syphilis

Legislation Regarding the Venereal Diseases.—An analysis[187] was made, under the auspices of the World Health Organization, of the venereal disease legislation of 44 countries. There are considerable differences in the laws examined, especially in the extent of the powers and the variety of the duties of health authorities. While in some countries epidemiological investigations are carried on by the health authorities themselves, in others these are the responsibility of medical practitioners and the health authorities intervene only when called upon to do so by practitioners. The important advances in the modern therapy of venereal diseases do not appear to have influenced legislation on venereal diseases at present in force (but there probably will

be some changes [Eds.]) although it might have been expected that these advances would have influenced provisions relating to defaulters and compulsory hospitalization. The venereal disease legislation varies from country to country (or state to state in the United States [Eds.]). In some the law covers only syphilis and gonorrhea; in others both these diseases as well as the other venereal diseases. There are few laws making provision for mass examinations as a control measure. Venereal disease continues to occupy a special place in health legislation despite the fact that the present tendency is to treat it in the same manner as any contagious disease.

Prostitution.—An exposition of the social approach to the solution of the problem of prostitution is presented by French.[188] From her studies the author concludes that there is no such thing as a "type" of girl likely to become a prostitute, that, while much is known of the unsuccessful prostitutes (those who have fallen into the hands of the law) little is known of the successful ones, who have never been apprehended. Inadequate sex training of wives, poverty, and the struggle for individual and feminine freedom are all factors. There is a definite link between prostitution and crime, but these are by no means the only reasons why women become prostitutes. Remedies are suggested such as jobs, recreation, and concentration on efforts to rehabilitate the younger prostitutes. If it is made more difficult for men to gain access to a prostitute, the practice would be greatly reduced.

Venereal Disease and the Homosexual.—In a most interesting study of 1000 consecutive male patients with gonorrhea or early syphilis who attended the St. Mary's Hospital clinic in London, in 1954, Jefferiss[189] found 8.4% admitted recent sexual contact with another male; 10.7% of the white patients, 15.7% of the unmarried white patients, and 23.2% of the unmarried white nonmanual workers admitted recent homosexual practices. There was a predominance of clerks, shop assistants, waiters, and those employed in the artistic trades in the homosexual group. Jefferiss discusses "congenital" and "acquired" homosexuality and feels that psychiatric treatment is unavailing in this condition. No mention is made of the role of the female homosexual in the dissemination of venereal disease.

Control of Syphilis in Industry.—Downing,[190] in considering the present problem of syphilis in industry, states that with a reservoir of about 2,000,000 persons in the community needing treatment, with 156,099 persons reported in 1953, and considering the sexual mores of our people, syphilis will remain with us for some time to come. In industries where members of the higher socioeconomic groups are employed, the discovery rate will be smaller than where members of lower socioeconomic groups are employed. But even in the industries in which only few cases are discovered, Downing considers the cost of finding even these few worthwhile to the industry. The need is stressed that management must be educated regarding the employability of syphilitics or persons found to have a reactive serologic test for syphilis who have no medical defect that would prohibit them from carrying out assigned duties. The certificate of a physician that the seroreactive person is noninfectious and physically employable should be sufficient. The employability of a person with a reactive serologic test for syphilis should not be determined by lay persons who pass on the other qualifications of the prospective employee.

Prevention of Venereal Disease.—A Sociological Approach: The present British Army preventive policy is based essentially on an educational one. Continence is the only sure method of preventing venereal disease.[191] Suppression of the natural sexual instinct is possible without injury to health. Sublimation can be obtained by concentration on games, general physical fitness, military duties and obligations, literature, and hobbies. Officers in the armed forces are faced with problems of dealing

with persons of diverse social levels. If the premises are accepted that the total sexual outlet varies little in regard to time or in regard to change in mores and the adult pattern is largely fixed in the late teens, it is time to appraise the current policy in regard to the prevention of venereal disease.

Investigation of Venereal Disease Contacts in U. S. Armed Forces.—Fiumara [192] describes the results of investigation of contacts reported in Massachusetts in 1954 by military personnel infected with venereal disease. The reduction of the infectious reservoir in the community, both military and civilian, occupies most of the venereal disease control officer's time. It includes finding the infected persons through screening tests; voluntary reporting, which is the fruit of education, and last, but most important, discovering hitherto unknown cases through contact interviewing and immediate investigation. Modern treatment with penicillin and the other antibiotics rapidly reduces the infectiousness of these patients and, given adequate time and effective dosages, will cure them.

Clinical and Pathologic Aspects of Premature Perinatal Death.—The wartime increase in incidence of syphilis (1944-1946) is shown by Anderson and Nesbitt [193] to have been no greater among the nonwhite than among the white population when increase in total population is considered. The control procedures in use at that time failed to avoid this increase; many possible reasons are discussed, but no conclusion is reached regarding them. The tendency of rates for early congenital syphilis to become stationary suggested the "steady state" criterion; but in early syphilis, the rates of only a few groups, e. g., the white 15-24 and 25-34 age groups, have remained nearly constant since 1951, so that the criterion is considered invalid, as far as the presented data are concerned. The control of syphilis in New York State is far from an accomplished fact. Two aspects of control in order to induce a continued downward trend are recommended: Systematic efforts to locate the population groups most at risk of acquiring the disease by intensive epidemiologic studies and by intensified control procedures in the groups thus isolated, such as contact investigation and health education programs especially adapted to these groups and the removal of any barrier to prompt medical treatment.

Venereal Disease Control in New York City.—According to Rosenthal and Vandow,[194] there has been a reduction in syphilis, gonorrhea, and other venereal diseases in New York City since the end of World War II. The public health control programs have combined community resources to include in the venereal disease combat teams the private practitioner of medicine; personnel of hospitals and clinics; educational institutions; social and welfare agencies; the voluntary organizations, such as the New York Tuberculosis and Health Association, Inc., and the American Social Hygiene Association; the clergy, and the Armed Forces, coordinated by the official health agencies and with, above all, an informed public. Further reductions in venereal disease incidence will be difficult to achieve in an area such as New York City, which is not only a focal point for traffic from all parts of the United States, but, in addition, is a global seaport and airport. Population movement from within the country, coupled with increasing international traffic into the area, constitute problems beyond any local public health control. These and other special problems peculiar to a large metropolis indicate the necessity for maintaining a vigorous program for the continued control of venereal disease.

Multiphasic Screening.—Breslow [195] reviewed the results of 16 multiphasic screening projects carried out in California during the years 1948-1954, inclusive. Serologic tests for syphilis were performed in 6 of the 16 projects. The serologic tests are considered still a useful part of the battery of tests in certain segments of the population, e. g., longshoremen and migrant laborers.

The functions of multiphasic screening in relation to public health are described in some detail.

The advantages and drawbacks of multiphasic screening programs in general are discussed by Holmes and Bowden.[196] Results of a multiphasic screening project in Richmond are reviewed and are compared to results of other such surveys. Fifty new cases of syphilis were detected during the Richmond project in 1950. Presence of syphilis has varied on final diagnosis from 0.8 to 43 per 1000 persons screened in other projects.

Collen and Linden[197] present a review of the evaluation by multiple screening tests of 1000 members of the Kaiser Foundation Health Plan in 1952. Of the 1000 members screened for syphilis by the VDRL test, 970 were negative, 21 were doubtful, while 9 were positive. Of the 30 reactors, 17 were retested. Of 4 persons with positive screening tests retested, 2 were positive, and of the 13 doubtful reactors retested, none was positive, and 3 were again doubtful. Including results of physical examinations as well as multiple screening, 9 of the 1000 screenees were found to have syphilis or its sequelae. Only 22.3% of the persons screened showed no abnormality whatsoever.

Mass Blood Testing Project.—About 21,000 persons in Cleveland were given blood tests for syphilis in May and June, 1954.[198] The purposes of the project were to find and bring to treatment people with untreated or inadequately treated syphilis and to educate the public to seek medical care when syphilis is suspected. The Cleveland Transit System publicized the blood-testing project in a folder which was placed in all buses. Newspapers and radio and TV stations gave publicity to the project. Through the project, 254 patients with untreated syphilis were diagnosed and brought to treatment, while 387 patients with inadequately treated syphilis were returned to treatment.

Taggart and his group[199] noted that of 15,178 persons in selected industries and trades in the District of Columbia who were given serologic tests for syphilis, 2408 had reactive or weakly reactive results. All but 74 of these were located and brought to examination. Two hundred six represented new cases of syphilis, and two hundred fifty-five were persons returned for more treatment. Of the 206 new cases, there was one case of primary, 24 of early latent, 177 of late latent, 3 of neurosyphilis, and 1 of congenital syphilis. Of the 255 cases returned for further therapy, 19 were early latent; 222, late latent, and 14, neurosyphilis. So far as the persons tested represent the employed population of the district, the venereal disease control problem is in other than "white collar" groups. More than 80% of the cases needing treatment fell in the three lowest paid occupation groups. From the number of cases discovered who were brought to or returned to treatment, it is surmised that many thousands of workers still need to have their syphilis discovered and be given treatment for their infection.

The theme of a study by Smith, Donohue, and Stuart[200] is the role of serologic tests in the control of syphilis in the United States. More than 200,000,000 blood specimens have been examined by health department laboratories alone since 1940, and, during the ensuing years, 3,942,000 persons with syphilis that was not detectable by clinical means have been brought to diagnosis and treatment by these test results. Figures are given on the savings in terms of manpower, earnings, and prevention of late syphilis, as well as the dramatic decrease in reported early syphilis during this period. The place of the serologic test in multiple screening, in hospital admissions, in preemployment examinations, and in selected areas with probable high incidence rates of syphilis is described and discussed. Examples of results of such surveys are included, both of routine and of selective types. Greater emphasis will be placed in

the future on the selective type of survey as the best means of uncovering the estimated reservoir of 1,921,000 persons with undetected syphilis who are in need of treatment. The false-positive serologic reaction has not been a serious problem in high prevalence areas, and the increasing availability of the T. pallidum immobilization test and the T. pallidum immune adherence test serves further to brighten this picture. The introduction of the T. pallidum agglutination test brings an even more promising outlook, as it will eliminate many of the technical problems incident to the use of the other treponemal antigen tests.

According to Degos and Fournier,[201] in the five-year period, 1950-1954, almost 600,000 persons were subjected to serologic test for syphilis by law in the Paris area. It is not clearly specified what social group was involved. Only 0.7% of these persons were diagnosed syphilitic. In 400 patients with strongly positive or positive STS and without a history or clinical manifestations of syphilis, the Treponemal immobilization test was performed and was positive in every instance. In 579 syphilitics found in the year 1954, clinical manifestations were observed in only 35. In extensive serologic testing over a 10-year period in France, Robin and his associates[202] found the following percentages of seropositivity in the departments of Loire and Rhone: Premarital STS 0.59%, 0.55%; prenatal STS 0.78%, 0.47%; prison population 2.79%, 2.33%.

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Infectious Diseases

Annual Review of Significant Publications

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In this 22d annual review, as usual, subjects of current importance have the most space. Antimicrobic therapy with its less desirable aspects and viral diseases come first. Bacillary infections, especially from Salmonella and Mycobacterium, hold wide interest. Infections of coccal origin, except for those caused by staphylococci, are controlled largely by antimicrobics. The mortality from pneumonia, for example, fell nearly 90% between 1933 and 1955; that from rheumatic fever and syphilis, almost as much. Puerperal septicemia, erysipelas, and mastoiditis seldom are encountered any more.[1,2] Virologists list the most important advances in 1956 as follows: further progress in the use of live viruses for vaccination against poliomyelitis and adenoviral infections, expanding use of tissue-culture technique for diagnosis and for the discovery of new viruses, increased knowledge of orphan viruses, the search for antivirotic agents and for oncolytic viruses, and the discovery of the infective ability of nucleic acid.[3]

Antimicrobic Agents

It is nearly 20 years since a new era in medicine began with the advent of therapy with antimicrobics of fungal origin. An indication of the magnitude of their present use is the sale of $260,000,000 worth in 1952, as compared with $40,000,000 worth of sulfonamide compounds.[4] As emphasized repeatedly in these reviews, much harm also has followed. Three British editorials are pertinent.[5-7] "If we were not so often and so uncritically anxious to do a bacteriological good deed where none is required, we should be far less likely to spread harm of a kind that it may soon prove impossible to control." "As many lives may be lost by the indiscriminate use of antimicrobials as by failure to use them when they are needed."[5] The present-day custom to use antimicrobial prophylaxis for clean surgical wounds has become heir to the carbolic spray of a former generation. It has complicated rather than solved hospital infections.[7] "Repeated warnings of the danger of toxic and allergic reactions, superinfections and increasing microbic resistance have been given so often by so many authorities that the exhortations are wearying to those who heed them."[5] Yet promiscuous use continues. Perhaps the same may be said about adrenal steroids used in infections to make patients feel better quicker. All too often a patient with an undiagnosed infection or a known one is given two or more antimicrobics and cortisone, "just to be sure." Advice to discontinue unnecessary therapy often is resented by physicians, by patients, or by their families.

It is important to know that the majority of infections dealt with in general practice are of viral origin, and no virus smaller than that of vaccinia, the largest of measured ones, is amenable to any form of therapy available at present.[8] In a study of 5781 home visits in a Vermont community during a year, most of 1375 infections were those of the upper respiratory tract. For 698 victims of minor respiratory tract disease, antimicrobics were used in 5, and complications requiring therapy developed in 3%. There were only 96 cases of bacterial pneumonia and 7 of appendicitis. Even though penicillin was given only when

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deemed necessary, it was used in 1214 patients, or 1 in 5 of the whole group. It was prescribed more often than acetylsalicylic acid or any other drug. Broad-spectrum agents were used 207 times, and sulfonamides, in 985 instances.[9] Relatively few bacterial infections amenable to antimicrobics are encountered in general practice, and an estimated wastage of 90% of the drugs still holds.

Woodward pointed out that despite the success from therapy with antimicrobic agents, other underlying disturbances often cause death despite bacteriologic cure. Certain microbes persist during or after therapy and give rise to relapse. The nature of injury to capillaries and of vasoreactor substances able to cause shock-like states are matters for biochemical and physiologic research.[10] The importance of host resistance was emphasized by Swift.[11]

Altemeier again criticized the unnecessary use of antimicrobic therapy in surgical practice and cited a number of cases of maltreatment. Patients with contaminated wounds should be given aqueous quick-acting penicillin, not repository forms. A list of surgical circumstances was given in which antimicrobics are indicated.[12] Coldrey recommended nonoperative treatment for patients with appendicitis who are seen after the first 24 hours of illness. He used a battery of several antimicrobics. Among 137 patients so treated there was only 1 death. Appendectomy was needed in attacks less than 24 hours old, but he wondered if all patients would respond to conservative therapy.[13] His proposal, no doubt, will raise many eyebrows. Mesenteric adenitis often is mistaken for appendicitis in children. If adenoviruses are a cause, the development of a rapid diagnostic test would serve to avoid unnecessary appendectomy.

Untoward Reactions.—The mortality from anaphylactic reactions to penicillin may be as high as 30%. Severe reactions may occur after oral or topical application or a skin-test and from contaminated syringes. The skin test is not a reliable indicator of hypersensitivity.[14] Harmful side-effects of therapy were reviewed elsewhere.[15, 16]

According to Becker, penicillin was removed quickly from the blood by the injection of penicillinase intramuscularly. The procedure may be of value in treating severe reactions to penicillin.[17] If its use is safe, it may be preferable to adrenoid hormones for the purpose. Colebrook raised the question if saprophytic staphylococci in the nasopharynx could liberate enough absorbable penicillinase to neutralize penicillin administered for other infections.[18]

New Antimicrobics.—At a fourth annual symposium, as expected, many more new agents were described: ristocetin, Sigmamycin, oleandomycin, Bryamycin, Amphomycin, vancomycin, nucleocidin, and alazopeptin,[19] to add to the 4000 already known. Carbomycin (Magnamycin), oleandomycin (Matromycin), and spiramycin (Rovamycin) are similar to each other in activity and to erythromycin in structure. They are less effective than erythromycin. Staphylococci acquire cross resistance after exposure to one of them. Phagocytin, an antimicrobic of nonfungal origin, was derived from leukocytes of rabbits. It is a globulin-like substance, different from lysozyme and properdin.[20] In editorial opinion, penicillin will do most of what any of the new agents will do unless the bacterium resists it or the patient is sensitive to it.[21]

Novobiocin.—The same agent is named novobiocin, Albamycin, Cardelmycin, Cathomycin, and streptonivicin. Reports of its clinical use appeared in the April, 1956, issue of *Antibiotic Medicine and Clinical Therapy.* There was general agreement of its efficacy against staphylococci and that the drug should be used only for staphylococcal infection. Since staphylococci acquire resistance rapidly,[22] indiscriminate use of novobiocin, no doubt, will lead to the development of resistant strains. Novobiocin, erythromycin, and vancomycin[23] at present are the most effective agents against staphylococci and other penicillin-resistant cocci.

Therapy often was disappointing. Staphylococci persisted in 8 of 25 instances near the conclusion of treatment. In a series of 75 cases, novobiocin was not as effective as penicillin is against pneumococci and hemolytic streptococci, and it had no effect on enterococci, Proteus, or Actinomyces. Untoward reactions occurred in 19%.[24] Editorial concern was expressed about the supposed ineffectiveness of novobiocin, or any other antimicrobic, which does not appear in large amount in the spinal fluid or urine.[25] Its presence in these fluids, however, is not important in the treatment of meningitis or renal infection; it is the amount which gets into the tissue by way of the blood that counts.

Nystatin (Mycostatin) was used with apparent success in the topical treatment of vaginal and cutaneous moniliasis. Lesions of thrush disappeared often in two or three days but sometimes not for three weeks at the time when spontaneous cure may be expected. Nystatin failed to influence the course of fatal systemic moniliasis in a patient who had received broad-spectrum antimicrobics over a long period.[28]

Remarks at the symposium cited encouraged a trend toward using combinations of antimicrobics for treatment.[29] Editorial comments, however, warned against this practice and feared that it would increase commercial exploitation of unnecessary, inferior, and undesirable agents. The great majority of serious acute bacterial diseases respond well to single drugs properly used.[30, 31] So far as reputed therapeutic synergism is concerned, one has to be convinced that two plus two equals five.

Topical therapy with antimicrobics should be limited to agents such as polymyxin, bacitracin, and neomycin, which are unsuited to parenteral use because of their toxicity but do not sensitize patients to other valuable agents which may be needed at some future time for serious infection. Topically applied antimicrobics penetrate inflamed conjunctivas but not the posterior segments of the eye.[32]

Bacterial Resistance to Antimicrobials.—In Rantz's experience over a five-year period, staphylococci, colon bacilli and Proteus bacilli became more resistant to one or more antimicrobics. Enterococci and Pseudomonas were uniformly resistant to most agents. Hemolytic and nonhemolytic streptococci retained their sensitivity. Resistant bacteria were most apt to cause infections acquired in hospitals, after diagnostic or therapeutic instrumentation and operation on the urinary tract, and in patients who have had previous antimicrobic therapy.[33] Similar observations were made by Kirby. Resistant bacilli were present in the urine of more than 10% of cultures and were present exclusively when indwelling cultures were in use.[34]

During the treatment of 56 patients with pneumonia, tetracycline and chlortetracycline were effective, but both caused side-effects. Staphylococcal enteritis, pulmonary moniliasis, and aspergillosis developed in three instances.[35] Antimicrobics are only one factor in the cause of pseudomembranous enterocolitis, but an increase in the number of reported cases suggests that the danger is increasing. The problem was reviewed by Newman.[36]

An infant of 6 months with a dermal infection was treated with chloramphenicol. On the 12th day of treatment fatal pneumococcal meningitis developed.[37]

Antimicrobic-Resistant Staphylococci.—It is believed generally that staphylococci have become progressively resistant to antimicrobics, largely owing to their widespread indiscriminate use, and that these resistant forms now are causing many more severe and uncontrollable infections than before. Dissent with this view arose. According to McDermott, staphylococci have not changed their characteristics and do not become resistant to penicillin during therapy. He doubted that staphylococcal infections are becoming more serious; if anything, less so. The greater incidence of staphylococcal infections as reported from many hospitals was most likely due to increased numbers

of susceptible persons brought about by a number of factors, as, for examples, those allowing the survival of patients with diabetes by insulin therapy, or serious operations like splenectomy, gastrectomy, or pulmonary resection; therapy with adrenal steroids, roentgen rays, or antimicrobics and repeated venepunctures, biopsies, and the like.[38] Despite these views, the validity of the many recent publications on the increased number of serious staphylococcal infections and of penicillin-resistant strains can hardly be questioned. It is likely that the use of antimicrobics is selecting a tougher race of these cocci than those with which we had been familiar.

It was the impression of White and Knight also that patients with progressive, severe underlying diseases at present are more commonly subject to staphylococcal invasion. Agents used in therapy, such as mechlorethamine hydrochloride (nitrogen mustard) or steroid hormones, reduce resistance to infection. Sites of needle punctures, inlying cannulas, and bedsores are likely sites of invasion. A shift from drug-sensitive to drug-resistant infections was characteristic in patients who received antimicrobic drugs.[39]

Knight and White found ample evidence in hospitals of the increasing numbers of staphylococci resistant to antimicrobics, even though staphylococci were not more prevalent. Certain strains developed increased resistance to tetracyclines during therapy. Among other methods of control, it was suggested that nasal carriers be treated with an ointment containing neomycin or bacitracin, agents which rarely are used for systemic therapy. The use of erythromycin and novobiocin should be restricted to the treatment of staphylococcal infections, in case new agents to attack these cocci are not discovered.[40] In one hospital the incidence of wound infections with penicillin-resistant staphylococci increased in the five years before 1954 but has decreased since then as a result of a more judicious use of antimicrobics and a program to prevent infection.[41]

According to Rogers, the incidence of staphylococcal bacteremia has not increased much in the past 15 years, but that of staphylococcal pneumonia has. Wound infections increased from 1% in 1949 to 10% in 1954. Staphylococcus apparently has replaced Pneumococcus as a terminal invader in recent years. The increased incidence was most striking in patients with other serious conditions, but it was difficult to ascribe this to an increase in the incidence of antimicrobic-resistant staphylococci alone. It is doubtful if new antimicrobic agents will improve the situation, but they have caused a serious therapeutic problem. Better methods of prevention are needed.[42]

English clinicians report on 18 cases of staphylococcal pneumonia among 122 consecutive cases of pneumonia. Forty per cent had had previous pulmonary disease. Penicillin was helpful in only six cases.[43]

According to Spink, a mortality rate of 80% in patients with staphylococcal bacteremia observed between 1952-1955 showed that the rate was no less than it was in the preantimicrobic era. Many of the strains were penicillin resistant, and even though they were sensitive to other antimicrobics, these were therapeutically ineffective.[44]

Newborn infants in hospitals rapidly became nasal carriers of antimicrobic-resistant staphylococci from contact with hospital personnel. In one study 30% of 60 infants became carriers before the fifth day.[45] Cultures of the nasopharynx made in premature infants revealed no growth in 80% to 90% in the first few hours after birth. Staphylococci were the first to appear, followed by a viridans Streptococcus, enterococci, hemolytic streptococci, and coliform bacilli. Staphylococci usually were resistant to all antimicrobics used. Therapy seemed to have only minor effects on the bacteriologic findings. Implantation and persistence of hemolytic streptococci were not prevented by sulfadiazine.[46]

An epidemic of staphylococcal enteritis affected 12 of 21 infants in a nursery. In four severely ill patients, skin lesions and

epidermolysis occurred.[47] An epidemic of staphylococcal pneumonia in another nursery resulted in eight deaths. It began as a series of dermal infections and was caused by a single strain of antimicrobic-resistant Staphylococcus. The epidemic was considered as one manifestation of the widespread increase of such staphylococci due to indiscriminate use of antimicrobics.[48] Penicillin-resistant staphylococcal infections involved 37% of infants and 13% of mothers after discharge from a hospital. Similar outbreaks were observed in five other hospitals in 1954 and 1955. Twenty-four deaths occurred. The findings indicated the need for better control of infection in hospitals.[49]

Garrod tested the antistaphylococcal effects of eight new antimicrobics. In the order of bacteriostatic action were micrococcin, erythromycin, novobiocin, antibiotic E129, cephalosporin P_1, and vancomycin. In the order of bactericidal effect were vancomycin, antibiotic E129, erythromycin, novobiocin, and spiramycin. Staphylococci did not develop resistance to vancomycin. Serum exerts an inhibiting effect on the action of novobiocin, and staphylococci rapidly became resistant. The agents should be reserved exclusively for the treatment of staphylococcal infections.[50] Four strains of staphylococci were rendered resistant to erythromycin, carbomycin, oleandomycin, spiramycin and streptogramin. There was cross resistance to all agents except to streptogramin.[51]

Penicillin-sensitive and penicillin-resistant staphylococci isolated from the same lesion may be of the same phage type, according to Fairbrother. He suggested a new view to account for developing resistance: the Staphylococcus formerly led a "wild" existence and produced penicillinase, but this function was lost by residence in man. Therefore, penicillin-sensitive staphylococci themselves are mutants, not the reverse. By exposure to penicillin, reversion to the penicillinase-forming original strain occurs. It is possible that antimicrobic-resistant variants, now so common, are in fact preformed mutants which grow out selectively in the presence of antimicrobics. They "are being restored to their original position by our malpractices." [52]

Studies made among primitive people never exposed to antimicrobials showed 19% to be nasal carriers of staphylococci, as compared with 30% to 50% as found in most civilized communities. None of 23 isolated strains was resistant to penicillin, as compared with 60% to 80% in places where antimicrobic therapy is rife. A few nonpathologic strains were resistant.[53] Such strains do exist naturally without exposure to antimicrobics.

From the evidence cited, there is little doubt about the increasing importance of antimicrobic-resistant staphylococci. According to editorial comment, "like the sorcerer's apprentice we are being caught in the tangles of our own mishandled magic and unless the stern warnings of the bacteriologists are heeded by clinicians we may indeed soon be powerless in the face of rapidly fatal and drug-resistant infections." [54]

Diseases of Viral Origin—Viral Infections of the Respiratory Tract

Adenoviruses.—Discovery of the adenoviruses that cause a large segment of minor disease of the respiratory tract opened a new field of endeavor. A number of heretofore undifferentiated diseases now can be extricated according to their causative agent and named, for examples, Type 4 adenoviral pharyngitis, Type 3 pharyngoconjunctival fever, or Type 4 adenoviral pneumonia. As may be expected, viruses of these diseases, of influenza, and of infections still unidentified cause varying numbers of epidemic or sporadic cases in different places and in different years, according to the prevalence of the causative virus. An epidemic of adenoviral pharyngoconjunctival fever affected 62% of members of an isolated camp.[55] In one community in England, adenoviruses caused less than 1% of infections and influenza accounted for 19%,

while in another place pharyngoconjunctival fever predominated.[56] Influenza A and B was uncommon in New York State in 1954-1955, but 80% of serums tested gave positive reactions to adenoviral antigens.[57] In an outbreak among military personnel in 1954, adenovirus Type 7 was the cause, and 16 patients had the severe form as a viral pneumonia.[58] Epidemics among civilians caused by Type 3 virus occurred in Germany.[59,60] Evans' conclusion that adenoviral infections occur chiefly in military personnel and rarely among civilians therefore must be modified.[61]

Sporadic cases in adults caused by adenoviruses of Types 2, 3, 6, 7, and 8 were observed. One patient had viral pneumonia. The author concluded that these viruses may be one possible cause of viral pneumonia indistinguishable from "primary atypical pneumonia,"[62] but these all are viral pneumonias.[63]

Two of eleven volunteers inoculated intranasally with Type 1 adenovirus developed pharyngitis. Preexisting antibody in the blood may have prevented infection in the others.[64] Bell had difficulty in interpreting the results of his experiments. Although the infection was transmitted to some persons, and others inoculated with noninfectious material developed similar symptoms. Infection was transmitted more successfully by swabbing the conjunctiva with the virus.[65]

According to Jawetz the presence of neutralizing antibody for Type 8 virus in blood samples of persons from many parts of the world suggests the widespread distribution of an agent which causes keratoconjunctivitis.[66] Type 6 virus was recovered from two patients.[67] In an epidemic among aged adults in a nursing home, antimicrobics had no effect on the disease.[68]

Several unidentified cytopathogenic agents were recovered from children with laryngotracheobronchitis or croup, and neutralizing substance against them in patients' serums pointed to them as the cause.[69] Similar agents from infants with croup caused spongy cytoplasmic changes in tissue culture.[70]

In a search for adenoviruses during epidemics, infections with Type 1 poliomyelitis virus were discovered in three families. The only complaints were those of discomfort in the upper respiratory tract, vomiting, or malaise. Many had no symptoms. The isolated virus belonged in the attenuated end of the spectrum of pathogenicity of strains of poliomyelitis virus. In another family Coxsackie virus caused fever, headache, coryza, sore throat, cough, and pains in the chest or pleurodynia in seven of eight members. Six of serums tested showed a rise of specific antibody titer.[71] Without these studies the disease in each case would have been mistaken for a cold.

Adenoviral Vaccines.—Discovery of the adenoviruses paved the way for the development of vaccines. Stallones reported a 98% reduction of infections after adenoviral vaccination. Antibody titers as high as those which follow natural infection were evoked.[72] Formaldehyde-inactivated Types 3, 4, and 7 virus vaccine was injected into 4000 recruits, and 12,000 were kept as controls. Vaccination evoked neutralizing bodies and reduced the incidence of infections 50% to 75%, as compared with the control group. The recruits had already been vaccinated against smallpox, tetanus, typhoid, and influenza.[73] In earlier life they may have been immunized against pertussis, diphtheria, tuberculosis, poliomyelitis, and Rocky Mountain spotted fever; if they are sent overseas they are liable to receive dengue, hepatitis, yellow fever, encephalitis, pappataci, plague, cholera, Q fever, and typhus vaccine. Antimeasles vaccine soon may be prepared. How much immunization can a person tolerate?

It is probable that the adenoviral vaccines have the same limitations as those for influenza. The duration of induced immunity is short, its degree is unpredictable, the various types of virus are influenced only by homologous vaccine, and reactions to vaccine sometimes may be as uncomfortable

as the disease itself. At present, practicability of immunization would seem to be limited to the prevention of infections of closed groups in institutions, schools, military personnel, and the like.

Therapy. — Antimicrobics, as is well known, had no effect on the prevention or course of pharyngoconjunctival fever, nor had cortisone any effect on the ocular or nasal involvement.[55] In spite of this knowledge, it is surprising to read that oxytetracycline was given as standard treatment for adenoviral disease. In addition, expectorants were given.[58] There is no effective expectorant. The commonly used ones are nauseants that increase the flow of saliva. One can only comment that tradition is tenacious and that this form of therapy is an example of mumpsismus.

Over a three-year period 539 children with infections of the respiratory tract were divided into groups. Some were treated with sulfonamide drugs, some with penicillin, some with chlortetracycline, and the rest with a placebo as controls. Among 218 control patients, complications occurred in about 13%, as compared with about 15% in treated ones. In the control group the recovery time was 5.2 days; in the treated group, 7.6 days.[74] Obviously, antimicrobic therapy, if anything, is contraindicated in mild respiratory tract infections as repeatedly pointed out, but generally disregarded.

The Common Cold.—Despite much advertising publicity, investigations reported in two papers in the Nov. 24, 1956, issue of *The Journal of the American Medical Association* revealed no effect of bioflavinoids or ascorbic acid either in the prevention or cure of colds. Spicy editorial comment on the subject is pertinent.[75]

Isolation of the cause of the common cold has not been accomplished to the satisfaction of most investigators. According to Pollard, nasal washings from patients inoculated into the allantoic cavity of eggs caused an increase in the number of histiocytes in the allantoic fluid. Since similar changes followed the inoculation of influenza and mumps virus, it was assumed that a virus of the common cold did the same.[76] A virus obtained from a patient with typical symptoms was said to have been maintained through four passages in suckling hamsters. Inoculated hamsters had coryza and were immune to reinoculation.[77]

An epidemic of coryza affected a colony of chimpanzees. A cytopathogenic agent grew in tissue culture inoculated with secretions of a sick animal. The disease was induced in healthy chimpanzees by intranasal inoculation of tissue cultures. Blood from a laboratory worker who contracted a similar disease at the time specifically neutralized the virus. A number of his barrack mates also possessed the antibody.[78] Perhaps one or more of the agents causing the common cold are at hand. Outbreak of bovine rhinotracheitis occured in California and Colorado. A virus was recovered and cultivated in tissue culture, but no attempts were reported to determine its relationship to the agents of respiratory-tract disease in man.[79]

Viral Pneumonias. — Viral pneumonias usually represent the severest forms of a number of minor infections of the respiratory tract, many of which are caused by adenoviruses. Others most probably are caused by viruses still unidentified and are associated with the development of cold agglutinin.[63] A form of severe, epidemic, and sporadic viral pneumonia unassociated with minor infections occurs. In an outbreak of this kind, 27 of 108 pupils in an English school were involved in a month. None of the others had colds or sore throat.[80] In this respect the disease resembled the ones described by Daniels, in 1942, and by Kotin, in 1947. On the other hand, the favorable response said to follow therapy with chlortetracycline[80] suggests a cause other than viral, since antimicrobics have no influence on viral pneumonia, as shown in the past and again recently.[81] Another report of an epidemic in England was made. Agglutinin for Streptococcus MG was present in the blood of 19% of

168 patients; serologic evidence of influenza B, in 7%, and of influenza A, in 2%.[82]

An epidemic of bronchiolitis affected adults, infants, and young children in England, of whom 6% died. Absence of bacteria in pneumonic lungs at necropsy indicated a viral agent as the cause. An epidemic of colds was present in adults at the time.[83] No reference was made to studies of viral pneumonia in infants by Adams several years ago.

Influenza.—During an epidemic of influenza A among 664 boys in a school, 320 had been vaccinated with A and B strains. Among those vaccinated two years ago, 12% got influenza, as compared with only 2% of those vaccinated one year ago. The rate among unvaccinated students was 20%.[84] A soldier who had had a severe systemic reaction to influenza vaccine was reinoculated with vaccine a year later. Within three hours, signs of severe transitory encephalopathy and meningeal irritation developed.[85]

Influenza A virus sprayed into the throat of 17 volunteers failed to give rise to evidence of infection. Perhaps passage of the virus in chick-embryo cultures reduced its invasiveness for man. The authors cited unpublished data of Price in which 60% of volunteers developed influenza after intranasal inoculation. The experiments were made to test the immunizing value of the procedure.[86] Symptoms among volunteers inoculated with an agent causing colds were delayed and mild if their nasal secretions contained an inhibiting substance able to inhibit the growth af influenza virus in egg culture. The active component is heat-labile and trypsin-stable.[87] Evidently factors other than specific humoral antibodies influence susceptibility to viral infections. A fluorescein-labeled antibody applied to smears or slides of desquamated nasal epethelial cells and macrocrophages permits rapid diagnosis of influenza. The test, though quicker, is not as reliable as the hemagglutination-inhibition test.[88]

Serum of swine was known to contain antibody against influenza virus, and further study revealed similar antibody in the blood of chickens, rabbits, guinea pigs, dogs, cattle, and sheep. The patterns of immune bodies were similar to those present in children during the same period.[89]

Experiments in mice were performed to simulate the changes which influenza virus may undergo by residence in man during interepidemic periods. A strain of influenza A was passed in mice immunized against it, and a new variant form, As, appeared. Variant As passed in mice specifically immunized against it gave rise to Variant Ba. This process was repeated twice more. The resulting four variants had an antigen in common with the parent A strain, but differed from it by developing a progressively increasing amount of their own specific antigen. Their pathogenicity remained similar. The same kind of variation probably accounts for the natural instability of influenza virus and partly explains the difficulty in making effective vaccines.[90] Influenza virus, unlike the virus of poliomyelitis, is composed of loosely organized units containing a variable number of genetic determinants enclosed in a membrane derived largely from the host cell. In other words, a virus particle is like a bag full of different genetic units.[91]

Distemper, a viral infection of the canine respiratory tract, was transmitted experimentally to men by Nicolle and from men to dogs by Bryan. Adams demonstrated cross immune reactions between the viruses of canine distemper and of measles. Human blood samples were found to have antibody against distemper. Both diseases affect the respiratory tract and cause similar pathologic changes. The viruses may be related.[92]

Vesicular stomatitis, a viral disease of cattle, is transmissible to man. Among a group of persons who handled infectious material, specific antibody appeared in the blood of 54%. The disease may be mistaken for influenza or herpangina. Diagnosis was made by isolating the virus or by serologic test.[93]

Poliomyelitis.—According to a list prepared by the National Foundation for In-

fantile Paralysis, about 122 papers in the past year dealt with the subject.[94] A few are considered here.

According to a report in July, 1956, the incidence of poliomyelitis has decreased since 1952. In 1955 the case rate per 100,000 population was the lowest since 1947. An outstanding feature was an increase of infections and deaths in older children and young adults.[95] According to another report, the number of cases of poliomyelitis for the first quarter of 1956 was the same as in 1955, and the number of paralytic cases, 26% greater.[96]

It is of interest to consider for a moment the disproportionate amounts of money collected from public contributions for the study of poliomyelitis as compared with other far more important diseases.[97,98] Some of the figures are shown in the Table.

The incidence of poliomyelitis was studied over a period of years in 150 households. One hundred nine episodes of household infection were detected. Among "index" children and their close associates, an estimated 240 infections occurred, none with paralysis. In proportion to the population in the area, there was an estimated number of 77,000 infections and 109 reported cases of paralytic disease, or 1 paralytic victim to 700 of those with mild and inapparent attacks.[99] An epidemic of poliomyelitis in an apartment house occurred in midwinter. Blood samples tested by complement-fixation from 124 persons gave positive results in 44. Of susceptible parents of infected children, all but one became infected. The disease evidently is highly contagious. The complement-fixation test provided a method of rapid diagnosis.[100] In a study of 250 patients and household contacts, infections were detected in one-third of the families. One-third of persons in contact with victims had poliomyelitis virus in their stools. The rate was higher in persons who had some symptoms. Virus was present in stools of many household contacts and of patients for three weeks after recovery.[101]

Studies by Eklund and Larson, on an Alaskan island, showed that Type 3 virus caused an explosive outbreak in a nonimmune group. Most cases occurred in a two-week period and seemed to spread from person to person. Type 3 virus caused bulbar and meningeal involvement more often and attacked adults less often than other types.[102] Poliomyelitis is widespread in the Amazon basin and in the Middle East, according to the prevalence of neutralizing antibodies as discovered in surveys. Serologic evidence of infection was found chiefly in the younger age group, in contrast with studies in more highly developed regions.[103]

An official investigation in England left no doubt that vaccination against diphtheria and pertussis predisposes children to poliomyelitis. The risk was greatest with alum-precipitated diphtheria-pertussis vaccine. Plain pertussis vaccine was comparatively safe, and smallpox vaccine did not provoke poliomyelitis. An estimated 13% of paralytic cases in children up to 2 years old was causally related to the procedure. Only 2% of older children were affected. Vaccination not only may incite poliomyelitis but also determines the site of paralysis. The mechanism is unknown.[104] In another study, poliomyelitis in three of five children developed in the limb injected with vaccine. Vaccination did not incite the disease in two other children whose stools also contained Type 1 virus.[105]

Sabin reviewed the evolution of knowledge about the pathogenesis of poliomyelitis. Much confusion arose by using different strains of virus in different animals in experimental studies. At present it seems

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Incidence of Diseases Compared with Public Contributions for Study of Each

Disease	Relative Incidence	Money Collected, Millions
Poliomyelitis (reported cases)	1	$66.9
Muscular dystrophy	2	3.9
Tuberculosis	4	24.7
Cancer	7	21.3
Mental disease	25	1.5
Arthritis	75	1.8
Heart disease	160	11.3

ingested virus attaches itself to the mucosa of the nasopharynx and intestines, where it multiplies. From here it enters the regional lymph nodes and overflows into the blood. It is then taken up by cells of the reticuloendotheleal system. Some strains multiply and cause viremia, others do not. Virus may then relocalize in the alimentary mucosa. From various sites of growth the virus invades sympathetic and sensory peripheral ganglions, and if it is highly neurotropic, further invasion of the central nervous system occurs. Antibody probably exerts its effect on the neural sites of multiplication by preventing secondary localization of virus in other tissues and reducing the extent of invasion of various peripheral ganglions.[106]

Vaccine.—Statistics do not always agree. As mentioned before, the number of cases of poliomyelitis in the first quarter of 1956 was the same as in 1955. According to the National Foundation report, 10,000,000 children were vaccinated in 1955, and the procedure was said to be 80% effective.[107] Other statistics suggest that the use of vaccine caused a sharp drop in the number of paralytic cases, especially in children aged 7 and 8, but that optimism should be tempered for several years.[95]

Vaccination of a large controlled population was done before and during an epidemic. The attack rate was lower in vaccinated than in unvaccinated persons, but the difference was not significant statistically. There was no evidence that vaccination caused poliomyelitis.[108]

The present use of vaccine should not be regarded as the best method to prevent poliomyelitis. It is uncertain how long protection lasts and whether artificial immunization of children will insure them against the risk they eventually will face when as young parents they may be exposed to infection from their own children. It may be desirable after vaccination to give subsequent feedings of live attenuated viruses for the purpose of keeping immunity at an effective strength.[109]

Further studies by Koprowski and his co-workers showed that feeding attenuated strains of virus together with the intramuscular injection of human-immune-serum-globulin evoked antibodies without causing illness. Type I virus did not appear in the throat but was excreted in the stools of every subject.[110] Homotropic antibody was demonstrable for seven months.[111] Vaccination with virus killed with formaldehyde had no significant effect in influencing intestinal infection. Virus was isolated from the stools of 52% of vaccinated persons exposed to infection and from 67% of unvaccinated ones.[112] Sabin revised his adverse opinion about the value of the Salk type of vaccine, since it does not interfere with alimentary infection induced by feeding attenuated viruses. Perhaps a more durable immunity will be provided.[113]

In three papers in the Jan. 12, 1957, issue of the *British Medical Journal*, Irish investigators cast serious doubt on the safety of oral vaccination. Attenuated viruses TN Type II and SM Type I indeed caused no significant illness, and antibody was evoked in the majority of vaccinees, but all of them excreted the respective viruses in their stools, and these invaded other nonvaccinated family members. There was ominous evidence of reversion to virulence of both fecal viruses when paralysis developed in inoculated monkeys. The viruses evidently went in as lambs and came out as lions. Because of the reversion of the viruses to virulent forms, and because they spread to other people, the authors do not regard them as suitable for human vaccination, since the fecal viruses did not differ much from naturally existent ones. An ideal vaccine-virus should not cause disease, should not be transmissible to other persons, should not multiply in the throat and, of course, should stimulate effective immunity. No one can predict what may happen if a community is seeded with a transmissible avirulent virus that may revert to its original invasive form.

Other Studies.—In studies on hamsters, the incidence of paralytic poliomyelitis depended upon a number of factors. Inoculatory trauma when virus was injected into the brain, activation of virus in the blood by cortisone, environmental conditions causing stress, and diet had an influence on inciting the disease. As in many other infections, disease often was conditioned more by temporary changes in the host than on the pathogenicity and invasiveness of microbes.[114] Castrated male hamsters inoculated with virus often developed paralytic poliomyelitis while normal ones were refractory to infection. Susceptibility was highest immediately after castration and was reversed two weeks later.[115]

A new, simple, rapid microtest for typing and assaying the viruses of poliomyelitis was devised. It is a specific floculation reaction resulting from the mixture of virus and homologous antibody. It may be of value in diagnosis, typing, standardization of vaccine, epidemiology, and for other purposes.[116]

An antimicrobic agent, helenin, had prophylactic value in monkeys but not in mice inoculated with poliomyelitis virus. Its action may be similar to that of another agent, called M5-8450.[117]

Viral Hepatitis.—Between 1950 and 1955 the number of reported cases of viral hepatitis increased from 2820 to 50,093. An actual increase in the number may have occurred, but it is likely that awareness of the disease, better diagnosis of mild cases, and better reporting largely were responsible. The peak incidence was in late winter or early spring. The death rate was rather constant and suggested that deaths mainly occur from nonseasonal serum hepatitis.[118]

Oysters were the source of an epidemic affecting nearly 700 persons in Sweden. The incubation period lasted between 21 and 32 days, and the time of appearance of jaundice, from 27 to 41 days.[119] Serum hepatitis developed in 15 patients after dental procedures involving the penetration of mucous membrane. The need for sterile technique was emphasized.[120] Even if instruments are sterile, trauma may activate a virus present in the mouth as a commensal.

An unusually severe endemic and epidemic form of hepatitis was observed in Peru. In a series of 43 cases, 36 ended in death. It was not highly contagious, and the course usually was afebrile. The hepatic lesions were similar to those of viral hepatitis,[121] yet in no other reported studies had the death rate been so high. It is possible that the majority of mild or inapparent attacks went unrecognized, or perhaps yellow fever or a poison should have been suspected.

In an epidemic in a mental hospital, γ-globulin failed to prevent the disease in other inmates, as compared with similar ones not given injections.[122] Official recommendations for the prevention of hepatitis emphasized the dangers of infection from transfusion of blood, injection of plasma, undetectable carriers, contaminated instruments, and other important factors but omitted mention of the use of γ-globulin. The name viral hepatitis was used, but it was stated cautiously that the disease is "believed to be caused by viruses."[123]

A virus obtained from the blood of patients with viral hepatitis was cultivated in tissue cultures. Serum obtained from a person who had had the disease neutralized the virus. It was cultivated from the serum three months after recovery of the patient. The possibility that the virus came from an extraneous source was not proved.[124]

Varicella.—Several investigators called attention to systemic involvement during chickenpox. In one study, of 453 patients, the respiratory tract was affected in 41, or 9%. A viral form of pneumonia occurred in 16% of adults and in 5% of children. Antimicrobic therapy had no effect on the disease. Bacterial superinfection usually caused by Hemophilus influenzae was rare and noted only in children.[125] In two other reports, 28 cases of varicella pneumonia were described. Three adults

died. Roentgen shadows were characteristic but not specific.[126,127]

Antismallpox Vaccination.—Jet injection of antismallpox vaccine made from lyophilized suspensions of infected chorioallantoic membrane of hen's eggs was a rapid, simple, satisfactory procedure.[128] Complications of antismallpox vaccination occurred in 60 (0.9 per 100,000) of over a half million primary vaccinations. They were classified as inoculation vaccinia, eczema vaccinatum, gangrenous vaccinia, fetal vaccinia, postvaccination encephalitis, and vaccinational exanthema. Several deaths were caused. Specific immune γ-globulin is available for prophylaxis in Sweden.[129]

Mumps.—Striking improvement was reported within a few hours in severe cases of mumps orchitis after treatment with cortisone.[130-132] On the other hand, although swelling and pain were lessened in five other patients, the duration of swelling was unaffected. In three patients, orchitis developed on the opposite side during therapy, and the course of parotitis was uninfluenced.[133] Evidently cortisone, as stated before, may make patients feel better quicker, not to mention certain risks involved.

Presternal edema was observed in 1% to 6% of patients and probably was caused by obstruction of the lymphatics by the swollen submaxillary glands.[134] Apparently mumps virus, like a number of others, may cause acute hepatitis. A case was described, and references to others were cited.[135]

Measles.—Two overlapping epidemics of rubeola and rubella were observed in the Falkland Islands. Twenty-one persons who presumably had had both rubella and rubeola in 1948 had rubella again in 1952. Between the ages of 15 and 45, many more women than men were sick. Relapses were common, one-third of 144 patients had no exanthem, arthralgia occurred, and congenital defects appeared in infants as expected.[136] In a 10-year period 24 cases of measles encephalitis were observed. In one instance characteristic evidence of measles was absent, and diagnosis was made by the presence of giant cells in the lungs and meninges.[137] It may have been caused by a different virus.

Two cases of measles pneumonia and two pneumonias of unknown origin were characterized by giant cells in the lung. Evidently such cells with either intranuclear or cytoplasmic inclusion bodies may result from infection by any of a number of viruses. Measles virus is one that specifically causes their appearance.[138] The successful cultivation of the virus of measles referred to in last year's review may lead to the development of a vaccine.

Study was made of the incidence of infectious diseases in a school over 56 years. Measles and mumps diminished greatly. The incidence of rubella and influenza was constant, and viral hepatitis, because of improved sanitation, almost disappeared. One outbreak of poliomyelitis occurred in 1936.[139]

Herpes Simplex and Zoster.—The virus of herpes simplex causes a wide variety of ailments besides the well-known labial eruption. There also occur gingivostomatitis; ocular, dermal, and genital involvement; encephalitis, and lesions resembling generalized vaccinia. The virus is widespread in populations, and antibodies were demonstrable in 90% of people as a result of previous or persistent infection. Infection may occur despite the presence of antibody.[140]

Siede suggested that the virus of herpes zoster may cause a form of viral hepatitis. Seven illustrative cases were cited.[141] If this be the case another virus may be added to that of yellow fever, viral hepatitis, mumps, and mononucleosis as a cause of hepatitis.

Viral Encephalitis.—An epidemic of Eastern equine encephalitis among horses and mules in Massachusetts in 1955 was the first since the 1938 outbreak. In also involved pheasants in four aviaries. Several cases among infants and adults were observed. Probably the virus is enornithotic in wild birds and is transmitted by mites, lice, and mosquitoes. Climatic conditions favoring mosquitoes are associated with an

overflow of infection into equines and humans.[142] The discovery of the virus of Western equine encephalitis during the winter in hibernating mosquitoes helps to explain its perpetuation from year to year in its natural hosts.[143]

The virus of Japanese B encephalitis was recovered from the brain of a soldier who developed encephalitis in this country 11 days after leaving Korea.[144] Another exotic infection occurred in Brooklyn as a case of epidemic hemorrhagic fever.[145]

The virus of encephalomyocarditis, which is related to Columbia SK, MM virus, and African Mengo virus, was recovered from two captive primates and from a wild squirrel in Florida.[146]

A dead antirabic virus vaccine prepared in duck eggs in place of rabbit-brain tissue may avoid some of the dangerous side-effects previously encountered. Allergic reactions, however, still occurred. Detectable antibody was evoked in 7 to 10 days after the first injection in volunteers.[147] Antirabic vaccine caused polyneuritis in two persons.[148]

Four species of insectivorous bats in the southern United States were naturally infected with rabies virus. Some of them also harbored a virus similar to that of St. Louis encephalitis. Any wound caused by a bat bite should be regarded as a possible exposure to rabies.[149]

Coxsackie Disease.—Studies on 125 patients in a hospital included 48 with disease presumably of viral origin. Of these, only four were caused by Coxsackie virus Group B. There were meningeal symptoms in three and pleurodynia in one. A virus of Group A may have been the cause of encephalitis in one patient. Evidently Coxsackie viruses were not widespread in that community.[150] Canadian physicians isolated Group B Type 4 virus from the spinal fluid of three patients with meningitis.[151] Group B virus caused 20% of acute viral encephalitides in Toronto.[152] An infant infected prenatally and delivered by cesarean section died from meningoencephalitis and myocarditis caused by virus Type 3. The mother had had what seemed to be a cold accompanied by vaginal bleeding in the 38th week of pregnancy.[153]

Cortisone injected into adult mice infected with Coxsackie virus caused extensive myocardial necrosis, as compared with minimal changes after either agent was administered separately. The possible conversion of benign Coxsackie disease of humans into a serious infection if cortisone be given must be considered. The cardiotropic nature of B-3 virus suggested its causative relation to a form of myocarditis in infants.[154]

A "New" Clinical Entity.—An epidemic mild infection characterized by meningitis, an exanthem, fever, nausea, vomiting, oral lesions, and slight general adenopathy occurred in England in 1956. Many children were affected. An agent probably related to Coxsackie virus Group A may have been the cause, since a neutralizing antibody was present in eight patients tested. The disease was similar to the one described by Neva, in 1954, except for the presence of meningitis.[155,156] In the same journal another similar epidemic was described, but in this one severe myalgia was outstanding.[157]

Apparently a new clinical entity is emerging. A disease or group of diseases not caused by poliomyelitis, Coxsackie, or other known viruses is characterized by injury of the nervous system, myalgia with paresis, emotional residuals, normal spinal fluid, involvement of the reticuloendothelial system, a protracted course, and a usually favorable outcome. It may be preceded by a mild infection of the respiratory tract. Outbreaks have been observed in Iceland, Africa, the United States, England, Germany, Belgium, and Australia. It is probable that others may be anticipated, especially in the late summer and autumn months. The subject was presented in three papers and a leading article of the *Lancet* of May 26, 1956. In one outbreak hospital personnel was affected, patients were not.[158] Until the cause is discovered the name "benign, myalgic encephalomyelitis" was proposed. ECHO virus Type 9 may be the

cause.[159] An epidemic probably of different origin in West Africa affected 31 observed patients, of whom 12 died from encephalomyelitis.[160]

According to Bodian, paralyses of cranial nerves, especially the facial ones, often is caused by the viruses of poliomyelitis, herpes zoster, and infectious mononucleosis.[161]

Viral Dysentery. — Five volunteers who had had viral dysentery were reinoculated 15 months later and no illness ensued. They apparently were immune. Because viral dysentery occurs repeatedly in some persons, it is probable that different antigenic strains of the agent or different viruses are the causes.[162] Higgins reviewed evidence substantiating the existence of viral dysentery.[163] Mild diarrheal diseases may be caused much more often by filtrable agents than by bacteria or protozoa.

Twenty-four cytopathogenic viruses were isolated from the stools of 56 children with acute gastroenteritis. Three were poliomyelitis viruses; three, Coxsackie viruses; two were ECHO viruses, and sixteen could not be identified. Shigella and Salmonella were present in 4 of 36 patients. Viruses were recovered from only 6 of 154 children without enteritis.[164] If the unidentified viral agents actually were causes of the diarrhea, they were a few among the many, as in similar diseases of bacterial or protozoal origin.

An outbreak of 18 cases of "winter vomiting" disease occurred in November in England, characterized by sweating, nausea, vomiting, headache, and vertigo, but not by diarrhea. Infants, children, and adults in a hospital ward were involved. It appeared to be an infection of the central nervous system, because 150 to 800 leukocytes were found in the spinal fluid. Serologic tests with antigens of nine known viruses gave negative results.[165] A similar kind of "epidemic vomiting" occurred in families and schools in Austria.[166] A few cases of "epidemic vertigo" were observed in adults who had prominent oculomotor disturbances.[167]

ECHO Viruses.—Perhaps some of the enteric, cytopathogenic, human, orphan viruses in search of a disease will get together, so to speak, with some of the diseases just discussed or others and cease to be called orphans. Two of them apparently have "found" their disease. In an epidemic of nonbacterial meningitis, ECHO virus Type 9 was isolated,[159] and in another, Type 6 virus was present in the stools of seven patients and in the pharynx of four. A specific antibody developed in each one.[168, 169] The adjective "aseptic" usually applied to meningitis in this connection is ill chosen; it means free from the germs of disease. Viral or nonbacterial are preferable terms.

A virus related to Type 4 ECHO virus was isolated from monkeys during an epidemic of rhinitis and from patients in an outbreak of enteritis (viral dysentery?). Viruses of Types 1 and 3 were found in patients thought to have poliomyelitis. Human γ-globulin contained antibody for all types except Type 2.[170]

ECHO viruses were more prevalent in the intestinal tract of children of a low economic group (8.3%) than in those more fortunate (3.1%). Ninety per cent of the viruses were obtained between June and October in a pattern similar to that observed with poliomyelitis and Coxsackie viruses. No illness could be connected with them. Whole families often were "infected."[171]

West Nile Virus.—This virus is widespread in northeastern Africa. In one area 61% of blood samples contained specific neutralizing bodies. The disease it causes may come in epidemics with peaks in midsummer. It is a self-limited, nonfatal, febrile one, occasionally with encephalitis. Mosquitoes and birds are the sources of infection.[172]

In Trinidad, immunologic tests on human serum samples indicated widespread residual infection with yellow fever, dengue, and ilhéus viruses. Yellow fever caused an epidemic in 1954.[173] A case of dengue was

diagnosed clinically, and the virus was established in infant mice.[174]

Boston Exanthem.—An epidemic exanthematous disease different from the delineated ones and probably caused by ECHO virus Type 6 was observed in Pittsburgh in 1954. It apparently was identical with the one described by Enders and Neva, in Boston, in 1951. Children had a rubella-like eruption; adults were more severely affected, but the rash was weaker. The incubation period was three to four days—shorter than that of rubella and rubeola. Multiple cases occurred in households. A cytopathogenic agent was recovered, and neutralizing antibody appeared in the blood. The name Boston exanthem was proposed,[175,176] but appearance of the disease in Pittsburgh shows that a limiting geographic name is as unsatisfactory, as in the case of Malta fever, Rocky Mountain spotted fever, or Haverhill fever. As an eponym, one may suggest, facetiously, nevenda or endneva for it, something on the order of hudihi or hidihu at one time proposed in England for viruses studied by Huebner, Dingle, and Hilleman and subsequently better named adenoviruses. By the way, what has become of Haverhill fever?

Disease of Probable Viral Origin

Infectious Mononucleosis.—An unusual case of mononucleosis with involvement of the central nervous system and no other clinical evidence of the disease occurred after prefrontal leukotomy. Atypical lymphocytes were in the spinal fluid, and the heterophile antibody appeared in the blood and spinal fluid. Perhaps infectious mononucleosis is another cause of puzzling cases of meningoencephalitis.[177] Cortisone seemed to be helpful in therapy of one patient,[178] despite the hazard of its use in viral diseases. The occurrence of seizures and other neurologic involvement was reviewed by Lazar.[179] A case of mononucleosis with extensive necrosis of the spleen and lymph nodes ended in death.[180] In another there was thrombocytopenic purpura.[181] Streptococcal pharyngitis may occur during infectious mononucleosis. The usual leukocytosis of a coccal infection may be masked. Diagnosis of coccal infection can be made by culturing the bacteria from the pharyngeal exudate, by an increase in the antistreptolysin titer and in the sedimentation rate of erythrocytes,[182] and by the presence of an exudate chiefly of polymorphonuclear cells.

A test dependent upon hemolysin for ox cells is said to be more reliable than the heterophil antibody reaction for diagnosis. Hemolysin appeared during the first week of illness, and its presence could be detected quickly and easily.[183]

Koyl reported 205 cases of what appeared to be a different viral disease of the reticuloendothelium. It began with symptoms of an acute upper respiratory tract infection and lasted 1 to 14 months. Asthenia and irritability were the outstanding symptoms; anorexia, depression, and aching were common. The lymph nodes enlarged, and pharyngeal lymphoid tissue was edematous. Splenomegaly was noted in 82. The blood cell count resembled that of infectious mononucleosis, but the heterophile-antibody test, made in only three instances, gave negative results. The infection may have been related to infectious mononucleosis or a modified form of it.[184] The duration was longer than in any other known viral disease.

Another "new disease" affected 30 persons in Harrisburg, Pa. It was regarded at first as a mild form of scarlet fever, but hemolytic streptococci were not the cause. One child had pneumonia. No cytopathogenic virus was detected.[185]

Cytomegalic Inclusion Disease.—Generalized cytomegalic inclusion disease was diagnosed in two infants. One died. In the other diagnosis was made by the presence in the urine of enlarged cells with typical cytoplasmic and intranuclear inclusions.[186] The disease was characterized by hemolytic anemia, jaundice, thrombocytopenia, and pneumonia. The so-called salivary gland virus, similar to one studied in 1923, by

Cole and Kuttner, was isolated [187,188] and may be the cause. It apparently persists in the body like the virus of herpes simplex and may give rise to inapparent and unrecognized overt illness. According to Weller, agents of this kind probably represent a group of newly recognized viruses. They may cause the disease in question or may be present only as commensals.[189]

There is question if the interstitial plasmacellar pneumonia of infants is caused by the salivary gland viruses or by Pneumocystis carinii, a protozoan parasite of rodents.[190,191] In Europe there is a widespread disease which seems to be caused by either Pneumocystis carinii or a fungus. Attempts to cultivate the agent were unsuccessful.[192] The matter awaits clarification.

Ten patients who recently had had myocardial infarction developed fever, pericarditis, pleurisy, and pneumonia. There was leukocytosis and an increased rate of erythrocytic sedimentation, but all cultures were sterile. Antimicrobic therapy was not beneficial, but cortisone and prednisone shortened the course. The cause is unknown, but the disease resembled idiopathic recurrent benign pericarditis.[193]

Experimental Viral Studies

Virotherapy of Cancer.—Thirty women with cervical carcinoma were inoculated with cultures of adenovirus. In 26 there occurred areas of necrosis and cavity formation in the central part of the tumor. Cortisone seemed to increase the degree of necrosis. The effects were less striking in patients whose blood contained antibody for the viruses. It is possible that the presence of antibody or its natural development in patients given inoculations neutralized the virus and inhibited its oncolytic action. In no instance, however, was the course of the neoplastic disease modified, and regrowth of the tumor occurred.[194]

The role of viruses in causing neoplastic diseases was reviewed. So far in man only warts and papillomas were found to be transmissible from person to person.[195] The tone of the editorial favored a view that most, if not all, malignant tumors are caused by filtrable agents, but no specific ones have yet been found.

Experimentally, roentgen irradiation may enhance or ameliorate the severity of infections. It was protective and beneficial in mice infected with the virus of lymphocytic choriomeningitis.[196] In an uncontrolled study, advice was given to treat pharyngitis, thyroiditis, parotitis, folliculitis, pancreatitis, bursitis, and hypertrophic lymphoid tissue with roentgen therapy.[197] There is no acceptable evidence that such therapy is beneficial in the treatment of these disorders, and thought must be given to harm which may be done thereby.

Tissue Culture in Diagnosis.—Advances made by the use of new techniques of tissue culture were reviewed by several authorities.[198-200] Application of the procedure, first to poliomyelitis, led later to the discovery of the adenoviruses, measles and ECHO viruses, and of many viruses present as commensals in animals.[201] Perhaps some of these represent the natural viral flora akin to the bacterial and protozoal flora harmlessly resident as commensals or saprophytes. Plans for the construction of a viral diagnostic laboratory were drawn,[202] and methods of diagnosis were described.[203]

Viruses may penetrate cells and remain in a dormant state. Changes in cells favoring multiplication of a virus depend upon the availability of essential nutrient substances on a high level of cellular metabolism. This may explain why a latent or a carrier state turns into actual infection if special factors alter or improve cellular nutrition. In a study with Miyagawanella psittaci, for example, phenylalanine and tryptophane were essential to growth of the organisms in tissue cultures, while other amino acids were not.[204]

According to Stanley, a virus may not be infectious because it does not leave the host cell and is duplicated only once during each cell division. Bits of protein may assemble around strands of ribonucleic acid

and form regular structures able to multiply in certain living cells. Under certain conditions, ribonucleic acid can cause infection without its protein overcoat.[205] Ribonucleic acid alone can induce an infected cell to cast off intact virus particles. There is evidence that the acid itself is infectious. Its effect is neutralized by ribonuclease.[206]

Significant increase in xanthine oxidase activity in the lungs of mice infected with influenza virus suggested a relation between purine catabolism and synthesis of virus, but further study showed the same to occur after chemical and bacterial injury. The increase in the amount of enzyme seemed to be related to injury and death of pulmonary tissue.[207]

Diseases Caused by Bacilli

Tuberculosis.—As in the case of pneumococcal pneumonia, a decline in the incidence of tuberculosis has not kept pace with the falling mortality rate. Since 1947 the number of new cases decreased 21%, in contrast with 64% in the number of deaths. At present, an estimated 55,000,000 Americans, roughly, one in three, are infected. More than a million have active or inactive disease, and of those, probably 250,000 are not under treatment and are infecting others.[208] About 80,000 new cases and 20,000 deaths are reported annually.[209] There is no reason for complacency. During World War II 6.7% of registrants for military service were rejected for tuberculosis, yet the disease developed later in 3 per 1000 of personnel. This incurred a cost of about 2,000,000,000 dollars for subsequent medical care.[210]

Since 1938, the incidence of pulmonary tuberculosis in men over 65 years old has risen from 50 to over 80 per 100,000. In women it remains about the same, 17 per 100,000. The increased incidence is due partly to discovery and diagnosis during roentgenographic surveys. Tuberculosis often is unsuspected in old persons, who serve as dangerous sources of infection. Forty-six per cent of patients had no symptoms referable to the lungs.[211]

On the other hand, the number of people sensitive to tuberculin has decreased from 35% to less than 10%, varying from less than 5% in some areas to 20% in others in persons 20 years old. A high proportion of new infections occur in those who react to tuberculin. According to Palmer, whose views differ from others, the tuberculin test is supplemental to roentgenographic survey for the early detection of tuberculosis.[212] In a survey of 87,000 English adults, pulmonary tuberculosis was discovered at the rate of 7.7 per 1000.[213]

Better methods of diagnosis and detection are needed. Roentgenograms visualize only two-thirds of the pulmonary area, and errors in reading films may approach 20% to 30%. The tuberculin test, though dependable, seldom is standardized. Laboratory tests often fail to reveal tubercle bacilli, and most of them may be killed by the pretreatment of samples for diagnostic inoculation of animals. The drugs in use for therapy are toxic, they are not bactericidal, and they often fail. The mode of therapy still is the result of trial and error.[214]

Treatment.—At a conference it was agreed generally that isoniazid combined with aminosalicylic acid were the drugs of choice for the treatment of patients with advanced disease. The addition of streptomycin served no useful purpose. Pyrazinamide combined with isoniazid was effective also, but cycloserine was inferior to the drugs mentioned. Free ambulation of patients during therapy seemed to have no harmful effect. No conclusion was reached as to the optimal duration of therapy except that prolonged treatment is desirable.[214] In the treatment of 3300 patients, those with multiple or large cavities or more advanced disease responded best to isoniazid and aminosalicylic acid; less well to isoniazid-streptomycin, and least to streptomycin-aminosalicylic acid. Each of the three two-drug combinations was equally effective for minimal tuberculosis. Studies on the use of cycloserine are under way. All of these agents are bacteriostatic, not bactericidal.[215]

Hinshaw saw little difference in the value of the several regimens used. Therapy should be selected for the individual patient and not established routinely. Daily rather than twice-weekly administration of streptomycin was preferable when it was combined with isoniazid.[216]

A less optimistic report was published. In a group of 30 patients with minimal disease, 15 were treated with collapse therapy or rest or both and 15 received streptomycin. After six years, of the 15 who had received no drug therapy during the first two years (7 subsequently received streptomycin), 11 were well. Of the 15 treated with streptomycin, 12 were well after six years. The results were said to show no striking advantage of antimicrobic therapy, although the author favors its use.[217]

Pathologically, antimicrobic therapy has altered the well-known lesions of tuberculosis. The overlying pleura, the capsules around the necrotic foci and the walls of tuberculous cavities are thinner; pulmonary fibrosis, empyema and destruction of pulmonary tissue is less, and the incidence of aneurysms in cavities and severe hemorrhage has been reduced.[218]

Therapy with steroid hormones in addition to streptomycin may reduce the signs and symptoms of tuberculosis, even when such treatment is harmful. Four events were described in which steroid therapy caused the development, reactivation, or aggravation of tuberculosis. All patients treated with adrenoid hormones must be observed continually to detect evidence of tuberculosis.[219]

Prevention.—The usual amount of BCG vaccine inoculated is too small to be of value. Immunization depends on the multiplication and persistence of bacilli in the vaccinee. Furthermore, since the *bacille Calmette-Guérin* was originally established, its various substrains or variant forms now used vary greatly in their immunizing properties. Fortunately, evidence of reversion to virulent tubercle bacilli has not been encountered, but a few fatal infections have occurred. Death ensued in vaccinated animals treated with agents that disturbed their metabolism. Vaccination always involves a calculated risk. This information was published in four papers in the November, 1956, issues of the *American Review of Tuberculosis and Pulmonary Diseases.*

Myers reviewed the pathogenesis of tuberculosis. He pointed out the danger of deception in evaluating the results of vaccination. No analysis of vaccinated persons has been made by differentiation between primary and reinfection types of tuberculosis. Most of the reports on the 100,000,000 vaccinated persons included so little after-study as to be worthless.[220] According to James, BCG vaccine is the most dangerous substance which has ever taken shelter behind the principle of protective inoculation. He supposed that its harmless reputation is based on the propagandist's axiom that if a statement is repeated often enough it will eventually reach the status of truth.[221] On the other hand, according to Aronson, of 3007 people observed for over 18 years, 13 of the vaccinated and 68 unvaccinated ones died from tuberculosis.[222] Who is right? There are highly effective measures besides BCG vaccination for the prevention of tuberculosis.[223]

Gauze face masks, like those customarily worn to avoid inhalation of airborne microbes, failed to prevent infection in 23% of rabbits during exposure in air laden with tubercle bacilli. Only 2% were infected when a more airtight cumbersome respirator was applied.[224] In many scientific essays, as in the one just cited, animals are said to be "sacrificed" instead of "killed."

Bacteriologic Studies.—By using special technique, 42 strains of Mycobacterium tuberculosis were classified into antigenic groups. Group I contained known "human" strains, one bovine strain, and one avian strain; Group II, bovine strains and one avian strain; Group III, mainly saprophytic mycobacteria.[225]

A variant form of strain H37Rv obtained after three years of growth in a synthetic medium was avirulent for animals

but served to immunize mice as well as strains H37Ra and BCG.[226] One of a variety of substances detected in the remains of disintegrated tubercle bacilli also was capable of immunizing mice against experimental infection.[227]

Much interest has arisen in forms of acid-fast bacilli different from M. tuberculosis. It is uncertain if antimicrobic therapy plays a role in the development or appearance of these unusual forms or variants. The recovery of acid-fast microbes—not M. tuberculosis, M. ulcerans, or M. balnei—from patients with chronic osteomyelitis, granulomatous lesions, and cervical adenitis was described. The lesions, clinical course, and roentgenologic, gross, and histopathologic evidence mimicked those of tuberculosis, and sensitivity to tuberculin developed. There was no proof, however, that the bacilli caused the lesions described. They may have been commensals, but their pathogenicity was suspected.[228] The matter is unsettled.

Seventeen cases of tuberculosis caused by a "yellow" antimicrobic-sensitive tubercle bacillus were described. At the time, four patients were well, four were still sick, five died, and three were lost to observation. "Yellow" bacilli seldom caused progressive disease in inoculated guinea pigs but did so in hamsters.[229] M. ulcerans and M. balnei caused dermal ulceration without systemic invasion. Inoculation of the footpads of mice caused severe swelling and may serve as a diagnostic procedure.[230] A simple test with cyanogen bromide was devised to distinguish tubercle bacilli of human origin from other mycobacteria. Only the human-type bacilli changed the color as a positive reaction.[231]

Relation to Sarcoidosis.—A patient thought to have sarcoidosis, because of the histologic nature of tissue from the bronchial mucosa, ocular lesions, and a negative tuberculin test, was found to have pulmonary tuberculosis. Recovery followed specific therapy.[232] Another patient with tuberculosis developed sarcoidosis, and the latter subsided spontaneously.[233] It would seem that tuberculosis may develop during sarcoidosis, may coexist, or, like histoplasmosis, may give rise to disease regarded as sarcoidosis.

The lesion caused by the inoculation of BCG vaccine in 10 patients with sarcoidosis was no different from that seen in other persons. The bacilli were recovered unchanged from the lesions after six weeks. Inoculation, as expected in sarcoidosis, failed to convert the tuberculin reaction from a negative to a positive one. Previous report of a peculiar response to BCG during sarcoidosis was not substantiated.[234]

Leprosy.—Interesting news emerged at a conference. M. leprae grew in HeLa-cell tissue culture. Ideas that leprosy is feebly contagious and that prolonged exposure is necessary were not substantiated. Many primary infections occurred after childhood, and the source of infection was more often outside than within family groups. There were 24 new cases in Texas in 1955, and the average age at onset was beyond 30 years.[235]

Leprosy appeared in a soldier four years after he had served in the Philippines in 1946-1947.[236] A lower rate of incidence among children since 1947 was noted in the Philippines. The decline may have been due to the general use of sulfone therapy or to other causes.[237] An epidemic of leprosy occurred in Nigeria between 1937 and 1948, but has diminished in incidence. The disease often was mild.[238]

Amyloidosis was the chief cause of death of lepers in this country. Renal involvement occurred regularly.[239] Electron micrographs revealed distinguishing morphologic differences between M. leprae and M. tuberculosis. M. leprae are seen as rods and filaments, dense spherical forms, as groups of "globi," and as groups of bacilli enclosed in a membrane. If pleomorphism were not due to degeneration, the bacillus seemed to have a complex life history.[240]

Salmonellas.—According to Savage, most cases of food poisoning are caused by sal-

monellas, and many of them are sporadic. The number of recorded cases is increasing. The cause was not found in 39% of outbreaks. Poultry seems to be the commonest source of infection, but pigs, cattle, rats, mice, cats, and dogs also are reservoirs. Infection is conveyed chiefly by meat, canned foods, milk, milk products, and eggs.[241] Three outbreaks were caused by S. newport in smoked fish apparently contaminated by polluted water used in preparation and poorly refrigerated afterward.[242]

Salmonellosis occurs at times during viral hepatitis and in other conditions. For example, in bartonellosis, a benign disease in Peru, S. typhimurium invaded 40% of patients, and most of them died.[243] Nine instances are reported in which nosocomial infection with Salmonella occurred months or years after gastric surgery; one was fatal. Diarrhea after gastric resection or vagotomy may be caused by the invasion of bacilli made possible by reduced resistance owing to the disturbed physiologic status.[244] Unsuspected bacteremia with Gram-negative bacilli occasionally occurred during severe hepatic disease and accounted for otherwise unexplained fever. Infection apparently was controlled with antimicrobics in four patients, but death occurred anyway.[245] Evidently reduction of resistance caused by various factors favors the pathogenicity of enteric bacilli. In children the onset of salmonellosis is more abrupt than in adults; leukocytosis is the rule, and the incidence of complications is high. In a series of 100 cases treatment with antimicrobics did not shorten the disease significantly.[246]

Cultures were made of hepatic tissue obtained by biopsy. Of 101 samples, bacteria believed to be contaminants were found in 13. The authors concluded that the normal liver does not contain bacteria and doubted that it filters micro-organisms from the blood.[247] Nevertheless, filtration may occur, and the bacteria may be destroyed and not detectable by culture. A case of pneumonia primarily caused by S. Choleraesuis was described.[248]

In the treatment of recurrence or relapse of salmonellosis, antityphoid-paratyphoid vaccine administered with chloramphenicol was said to have reduced the relapse rate to 1 in 20, in contrast to 1 in 4 in unvaccinated patients.[249]

Until now serologic diagnosis of infections with Salmonella has been practicable only when applied to typhoid. Neter and his co-workers developed a hemagglutination test for the detection of antibodies against other salmonellas, Shigella, and Escherichia coli.[250]

Typhoid.—Several hundred sporadic cases of typhoid occurred in the northern midwestern states in 1956. The causal bacilli were of phage Type E_1, but their source was not found. The wide distribution of victims and the absence of contact infections made this epidemic unique. If a similar one recurs, new methods will be needed to combat it.[251] An epidemic of 33 cases was caused by canned ox tongue probably contaminated during processing with water from a sewage-polluted river. Recognition of typhoid was obscured by the unwise use of chloramphenicol for victims of a coincident outbreak of influenza.[252]

The pathogenesis of typhoid was studied in chimpanzees infected orally. The feces contained no bacilli after 24 hours, and bacteremia appeared in 4 days, shortly before the appearance of clinical symptoms. In an animal killed after 96 hours, bacilli were present mostly in Peyer's patches, mesenteric lymph nodes, and the thoracic duct. Few were in the wall of the ascending colon, spleen, and peripheral lymph nodes; fewer in the blood, liver, and marrow, and none in the bile, feces, or bowel wall adjacent to Peyer's patches. Specific granulomas were present.[253] The observations confirm old theories of pathogenesis. Similar studies were made by Russians. Monkeys were fed cultures of paratyphoid B bacilli. After an incubation period of one day the disease was similar to that in man except for the absence of fever, and pneumonia developed in several. No reference to foreign literature was made. In another

experiment, special attention was given to the effects of typhoid "antigen" on the nervous system, a favorite site of Russian interest.[254,255]

*Shigellosis.**—In an explosive outbreak of gastroenteritis caused by Shigella sonnei, infection from suspected food caused symptoms within 15 to 70 hours in 78% of students in a school. Of those who ate the meal, 71.5% became sick and a few others carried the bacilli. None needed care in the hospital. Illness lasted 24 to 72 hours, regardless of antimicrobic therapy. Of 293 family members exposed to 109 infected children over a six-week period, only 28 (9%) had gastroenteritis.[256]

Floyd studied 226 episodes of mild diarrhea in Egypt. Only 30% were associated with Shigella. The disease seemed to be the counterpart of ones affecting many travellers in foreign countries and usually called gyppy tummy, acclimatizing diarrhea, or by terms indicating the region.[257] No mention was made of the possibility of a viral cause of some or most of these mild infections, although enteric viruses had been isolated from persons in Egypt. In Peking 30 years ago my similar investigation of mild diarrheas in American families rarely revealed Shigella or other known enteric pathogens and led to the eventual recognition of viral dysentery.

About 80% of patients with bacillary dysentery were "cured" with a five-day course of streptomycin given orally, as compared with 53% treated with a sulfonamide compound.[258] No untreated patients were reserved for comparison.

A British survey revealed the extent to which Shigella spread by patients may contaminate the environment. Bacilli were found on the hands, toilet seats, bedding, clothing, toys, floors, and in dust. S. sonnei survived for 17 days on toilet seats. Fecal-oral transmission was common among children.[259]

Escherichia Coli.—Two volunteers ingested heavy inoculums of E. coli of two serotypes, respectively. Gastroenteritis developed in both 7 and 17 hours later and lasted 32 and 46 hours. The bacilli were present in the stool, and a specific serologic response developed.[260] Apparently colon bacilli at times are pathogenic.

Smith reviewed the subject of septicemia in the newborn. In 15 patients of his series, infection in 10 was caused by E. coli; in 3, by staphylococci, and in the rest, by Pseudomonas aeruginosa. As a result of early diagnosis and appropriate antimicrobic therapy, only two died.[261]

By counting bacteria in urine samples and establishing a number higher than 100,000 per milliliter as a criterion of infection, Kass and Finland found a high incidence of symptomless infection of the urinary tract in women. Counts less than 100,000 per milliliter were disregarded as unimportant. The percentage of infection on that basis ranged from 6% among women attending an outpatient department for other reasons to 23% of women with cystocele. Indwelling catheters, instrumentation, and previous infections were common causes.[262] Chronic pyelonephritis, similar to that seen in man, was induced in rats by repeated intravenous inoculation of E. coli and massage of the kidneys through the intact body wall.[263]

Colon bacilli occasionally present in canned, frozen orange juice are of no epidemiologic significance. They apparently occur normally in the flora of orange groves and are present in fruit harvested aseptically. Coliform bacilli also were found in washtank solutions in fruit packinghouses.[264]

A shock-like state, vasomotor collapse, or circulatory failure often causes death in infectious diseases and also after the injection of contaminated blood or plasma, particularly when Gram-negative bacilli are involved. Cortisone is of doubtful value in therapy except perhaps in the Waterhouse-Friderichsen syndrome.[265] From experimental studies, vasomotor collapse caused by endotoxins of E. coli could not be ascribe to pooling of blood in systemic veins or, as commonly stated, to loss of

* Professor Shiga died in January, aged 86.

arterial or arteriolar tone. It seemed to be related to a fall in the cardiac output after a reduction in the return of venous blood to the heart. The events were traced to an initial alteration in the venous vasculature. Metaraminol and arterenol promptly reversed the hemodynamic failure.[266]

Brucellosis.—Small round densities seen in roentgenograms of the lungs of three patients proved to be chronic brucellar granulomas after surgical excision.[267] In a case of brucellosis diagnosed clinically as Hodgkin's disease there was hemolytic anemia and splenomegaly with large calcified nodules.[268] Evidence suggests that hypersensitivity to Brucella is of significance in the pathogenesis of the disease.[269]

According to Spink, bovine vibriosis may be approaching the incidence of brucellosis in cattle, but human infection rarely is recognized. Several instances have occurred in this country, and another was discovered in a meat-packing-house employee. Clinically the disease resembles brucellosis.[270] Spink's book contains a comprehensive survey of the field of brucellosis.[271]

Klebsiella Pneumoniae.—Klebsiella pneumoniae and Aerobacter aerogenes, being the same, should be grouped as Klebsiella and differentiated by Arabic numerals according to the 77 established specific types. Any one may be pathogenic. Types 1, 2, and 4 most often were found in the respiratory tract, and Types 7 and 19 in the urinary tract. In a six-month period Klebsiella was present in 24 patients with various kinds of respiratory tract disease. Some had classic pneumonia; others had unimpressive radiographic densities in the lungs associated with emphysema, tuberculosis, or cancer, and two had no demonstrable lesion. Klebsiella were in the respiratory tract of 2% of 200 healthy persons and in 11% of 70 with bronchogenic carcinoma. Types 2, 7, 8, and 1 were found in that order of frequency. Except in cases of typical pneumonia, it often was hard to decide if the Klebsiella present was the cause in order to prescribe proper antimicrobic therapy.[272] The mortality rate of klebsiellar pneumonia before 1948 was 73%; since then, 53%. Treatment with streptomycin and tetracyclines at present seems to be the best available, but with its use only 2 of 15 bacteremic patients survived.[273] In Erasmus' experience, typical gelatinous, bloody sputum was present in only 2 of 17 cases of pneumonia, and in only these 2 was a clinical diagnosis made. Each of his patients recovered. Treatment with streptomycin combined with sulfadiazine was recommended, substituting chloramphenicol if resistance increased. Early bacteriologic diagnosis is of paramount importance.[274]

Hemophilis Influenzae.—Thirty-eight family groups were observed for 21 months. H. influenzae and H. hemolyticus were found in the nose and throat of almost all persons exposed to patients; pneumococci were found in about 66%, and hemolytic streptococci, in about 50%. Infants rarely harbored hemolytic streptococci, but the incidence of carriers like that of H. influenzae increased with age to a peak at the sixth year and diminished. In early life pneumococci were found most often in the nose and throat.[275]

H. influenzae is an important cause of bronchiectasis in children. Treatment with tetracyclines, but preferably erythromycin combined with a sulfonamide drug, eliminated H. influenzae and pus from the sputum within two weeks in 23 of 27 children. Many relapses, nevertheless, were associated with H. influenzae.[276] The etiology of chronic bronchitis was the subject of a symposium. H. influenzae was the commonest pathogen present. Pneumococci were the cause in only 10% of cases. The hemolytic Streptococcus seldom was involved. The real cause seemed to be persistent irritation from polluted air and tobacco smoking. Treatment was disappointingly ineffective in preventing progressive changes. Antimicrobic therapy had not reduced the general mortality in the past 12 years.[277]

A bacillus called H. vaginalis was said to cause vaginitis and was present in 68 of 447 patients, often with Trichomonas and

Candida. In many instances there were no symptoms.[278] Before it can be accepted as a cause, proof is needed that the bacillus is not merely a commensal.

Other Bacillary Infections.—Dogs appeared to be primary reservoirs of Pasteurella tularensis and the principal disseminators of the lone-star tick in Arkansas. Of 136 dogs tested, agglutinin in high titer was present in the blood of 32%.[279]

Immunization does not always prevent diphtheria. A boy immunized in 1952 developed severe disease in 1956. During the four-year interval, immunity may have been lost. Other reports indicate failure of immunization in 25% to 34% of persons.[280]

Observations were made on 700 cases of tetanus in Brazil during a 10-year period. Therapy with the continuous intravenous injection of mephenesin (3-*o*-toloxy-1,2-propanediol), supplementary sedatives, antimicrobics, intravenous feeding, and small doses (100,000 I. U.) of antitoxin reduced the mortality rate to 18%. The previous rate after using sedatives and antitoxin had been 27%.[281]

Two unusual cases of endocarditis were described. One patient who recovered was infected with Erysipelothrix rhusiopathiae, the cause of swine erysipelas, after contaminating a superficial wound with soil from a pig farm.[282] The second instance was caused by tubercle bacilli implanted on the mitral valve after a surgical operation, and it ended in death from miliary dissemination.[283]

Bacillus anthracis was cultivated from the nose or throat of 14 of 101 mill workers who handled hair and hides.[284]

Diseases Caused by Cocci

Pneumococcal Infections.—Only 1 of 73 patients with pneumococcal pneumonia died after oral administration every 12 hours of 240 mg. (400,000 units) of phenoxymethyl penicillin. There were apparently no complications. The causative pneumococci were mostly of Types 1 to 8. Only one Type 2 strain was encountered. Austrian found little evidence of a decline in the incidence of pneumococcal pneumonia since the advent of antimicrobials.[285] Wagner cited a number of instances of delayed therapeutic response to penicillin. In the treatment of 24 patients with penicillin and hydrocortisone, a more rapid lessening of symptoms and fever was noted, as compared with 21 patients who received penicillin alone. There was, however, much less apparent difference between the two groups in the time required for the complete disappearance of complaints.[286] Considering this slight gain and the very low mortality rate reported by Austrian, it may be questioned if the risks of using hormone therapy, except in unusual circumstances, is justified.

Since penicillin was introduced, in one hospital the percentage of thoracic empyemas caused by pneumococci fell from 16.7 to 2.4. Postpneumonic empyema occurred as a result of delay in diagnosis or treatment of pneumonia, insufficient therapy, or the use of the wrong antimicrobic. The percentage of empyemas caused by staphylococci increased from 3 in 1929 to 55 in 1952. In infants 91% were caused by staphylococci.[287]

Years ago it was shown that Type 3 pneumococci were adversely affected by temperature higher than 37 C. New experiments indicate that hypothermia of 19 C induced for 24 hours in mice increased their survival time after intraperitoneal inoculation, as compared with controls. Supposedly, bacterial multiplication was inhibited to a degree greater than the diminution of an immunologic response of the host.[288]

Staphylococci.—An explosive outbreak of staphylococcal food-poisoning affected 244 of 306 exposed people. Symptoms began within six hours after a meal. Infection was traced to ham contaminated by a meat cutter with facial acne. It had been kept for several hours on a hot day before serving.[289] Staphylococci are less likely to be carried from a source to a recipient by

droplets of expelled nasal secretion than by indirect contamination of food, the skin, clothing, and bedding, as in the case of streptococcal infections.[290]

In rabbits phagocytosis of inoculated staphylococci and their transport by leukocytes accounted for the persistence of bacteremia. Staphylococci in the cells were protected from harm. More cocci were cleared from the blood of animals whose leukocytes were removed than from normal ones.[291] Host factors are important in controlling infections. Diabetes, cancer, leukemia, and operations on the prostate gland increased susceptibility to bacterial invasion, and males were affected twice as often as females. Septicemia occurred with both aureus and albus varieties of staphylococci.[292] Mild allergic shock induced in mice rendered them less resistant to staphylococcal infections than normal ones.[293]

Staphylococcal toxin injected intravenously into rabbits regularly caused spasm and collapse of the renal veins, renal ischemia, and, depending on the severity of the reaction, varying degrees of bilateral cortical necrosis.[294]

Staphylococcal Pneumonia.—Staphylococcal pneumonia in adults occurred chiefly during epidemics of influenza, and its incidence was low. Of 70 patients with pneumonia, only 4 had infection with influenza and staphylococcal pneumonia. Two of these died. Staphylococcal pneumonia occurred also in the absence of influenza,[295] as in instances I described in 1934. Of Hausmann's 18 severely sick patients, 6 had abscesses or empyema, and all recovered. Only six responded to therapy with penicillin.[296] According to Disney and his associates, any infant less than 2 years old with clinical signs of pneumonia or of pleural exudate has more than three chances in one of having staphylococcal pneumonia. Thirty-five cases, of which twenty-nine were primary pulmonary infections, were studied. Lung puncture was helpful in diagnosis. The mortality rate was 14%. Fourteen of twenty strains of staphylococci were resistant to penicillin. Erythromycin was used if there were resistance to other antimicrobics. The results did not indicate the superiority of erythromycin over other agents either alone or in combination.[297]

Streptococcal Infections.—In a study of family groups, about one-half to one-fourth of siblings in contact with a member who had hemolytic streptococcal disease contracted infection. Less than 1 in 20 of the parents were infected or became sick. Children chiefly between the ages of 2 and 10 were affected. Delay of more than two days in penicillin therapy of the patient who was the source was associated with an increased attack rate in exposed siblings.[298]

Hemolytic streptococci spread to 55 staff members and 57 patients in a maternity unit of a hospital. The majority were not sick, a few had mild sore throat, and two infants died. Treatment of some staff members with penicillin and tonsillectomy failed to rid them of streptococci. Reinfection from others was suspected. After isolation and penicillin therapy, streptococci were eradicated.[299]

Forty-eight children awaiting tonsillectomy were given sulphadimidine prophylactically for four months. During that time 25 acute unspecified infections occurred. Among similar children who received a placebo, there were 60 acute infections. The incidence of colds was the same in both groups. The author suggested that the prevention or treatment of acute streptococcal tonsillitis would reduce the number of unnecessary tonsillectomies at an age when susceptibility to tonsillitis begins to decline naturally.[300] [Sulphadimidine is the British equivalent of sulfamethazine U. S. P.]

In the experience of British clinicians, extraction of teeth preceded the onset of subacute bacterial endocarditis in 7 of 43 patients, or 16%. Two previous reports from American sources stated an incidence of 25%. Antimicrobic prophylaxis, or cover or umbrella, as it is called, failed to prevent immediate bacteremia after exodontia but presumably controlled it later.[301] Teeth are important sources of infection, but not the only ones. The degree of bac-

teremia after dental extraction is related to the trauma incident thereto. The percentage of positive blood cultures was highest within three minutes afterward and ranged up to 21%, especially if pyorrhea were present. Nonhemolytic streptococci and micrococci were found most often.[302]

Thirty-four cases of bacteremia without endocarditis caused by S. pyogenes, S. mitis and S. faecalis were studied. In some patients affected by S. faecalis, other Gram-negative bacilli or staphylococci also were present. Of the 34 patients, 13 who had concomitant other disease died. Since the advent of antimicrobics the incidence of streptococcal bacteremia decreased from 20 to 2 cases annually. Methods of therapy were outlined.[303]

In four patients with subacute bacterial endocarditis, murmurs became audible 18 days, 8 weeks, 2 months, and 3 months after the onset. Before murmurs were detected inadequate antimicrobic therapy only modified the infection. Early diagnosis was urged, and in case of doubt, when fever lasts more than a week, prompt intensive antimicrobic therapy is recommended even if murmurs are absent.[304]

Splenectomy for the treatment of subacute bacterial endocarditis is rejected by many clinicians. However, the operation was performed in three patients for whom antibacterial therapy failed, and remission followed in each. An infected infarct in the spleen was presumed to be the source of persistent bacteremia.[305] If this be true, cocci might also reside in other sites as well.

Febrile episodes, so common in leukemia, usually are regarded as characteristic of the disease, but in a group of 41 patients bacterial cultures were positive during 38 of 42 bouts of fever. Improvement without the use of antimicrobics occurred in 47%. The blood, the respiratory tract, and the ear were the most frequent sites of infection with staphylococci, Pseudomonas, and colon bacilli.[306] Perhaps in many instances bacteremia but not septicemia or infection was present.

Rheumatic Fever.—Prevention: It is assumed that 3% of infections by Group A β-hemolytic streptococci proceed to rheumatic fever, but this was not the case in Florida, where only 73 cases of rheumatic fever were reported in 14 months. Among 35,000 school children an estimated 40% harbored streptococci at some time, but a serologic response developed in only 20%. If, as in other parts of the country, 3% had developed rheumatic fever, 212 attacks would have occurred. Therefore the mere presence of streptococci was not the sole cause of rheumatic fever. The distribution of types of streptococci encountered was the same as found elsewhere. Type 12 Streptococcus was consistently present, but Types 1, 4, and 6 also were found.[307]

In 1946, one hundred sixty-seven patients with scarlet fever were treated with penicillin. Rheumatic fever subsequently developed in 12. Of the 167 patients, 100 were reexamined in 1953. Of the 12 who had had rheumatic fever, 8 had valvular lesions. According to the authors, and in contrast with general opinion, therapy of acute streptococcal pharyngitis did not suppress appreciably the development of rheumatic heart disease in the younger age groups.[308] On the other hand, the amount of penicillin customarily used 10 years ago probably would be considered inadequate now.

Controversy persists as to whether pharyngitis caused by hemolytic streptococci can be differentiated clinically from a viral infection. In epidemics of either, presumptive diagnosis without bacteriologic aid is reliable, but not in sporadic cases, because of the overlapping of signs and symptoms. The predominance of neutrophilic cells in the pharyngeal exudate caused by streptococci, in contrast with the mononuclear-cell exudate of viral infections, serves as a useful diagnostic aid,[309] as pointed out by Adams years ago.

In England, streptococci were isolated from 66% of 121 patients with sore throat. All were treated for four days with penicillin. Treatment shortened the duration of disease caused by streptococci by about 24

hours. No other beneficial effect was noted. Penicillin therapy suppressed a rise in the antistreptolysin titer and did not affect the convalescent carrier rate of hemolytic streptococci. The experience suggested that the risk of developing an initial attack of rheumatic fever was less than 1%, even without treatment with penicillin. Therefore prophylactic therapy was said to be of doubtful value in the age group studied.[310] Intramuscular injection of 1,200,000 units (720 mg.) of benzathine penicillin in 40 children convalescent from rheumatic fever caused fever in 12%, an increased sedimentation rate in 42%, and the appearance of C-reactive protein in 55%. These changes probably were the response of a foreign-body reaction, but an allergic influence may have played a role. The disturbance confused diagnoses as to whether or not rheumatic fever recurred.[311]

Other studies gave reason for more optimism. Oral administration of 150 mg. (250,000 units) of penicillin G twice daily for 10 days to school children caused a striking decline in the carrier rate and of clinical cases.[312]

In a follow-up study, only 60% of 444 children in a program of antimicrobic prevention of rheumatic fever were adequately treated. Of 213 children withdrawn from the program, only 19% were receiving prophylaxis. Reasons for incomplete success are failure of authorities to agree on recommendations, lack of cooperation by patients' families, financial reasons, and failure of appropriate education.[313] In another study, of 245 patients supposedly taking penicillin prophylactically after a streptococcal sore throat, 84 did not follow instructions.[314]

Of 100 patients with rheumatic fever, one-third received cortisone; one-third, corticotropin, and the rest were treated symptomatically. No significant differences were noted in the three groups as regards appearance of murmurs, pericarditis, or other cardiac changes. Serious bacterial infections developed in several patients treated with hormones despite the prophylactic use of penicillin.[315] In contrast with most other reports, Wilson and Lim observed favorable results in preventing cardiac injury during rheumatic fever by treatment with adrenoid hormones. Residual cardiac involvement had occurred in every patient between 1930 and 1955. In patients who received hormones 3 to 21 days after the onset of initial rheumatic fever, there was said to be no overt evidence of residual damage to the heart.[316] The matter obviously is unsettled.

Aschoff nodules were found in about one-third of 1180 auricular appendages removed during surgery on the heart. Rheumatic mitral valvular disease had been diagnosed in each patient, but all evidence indicated the process to be inactive. In one series, of 400 cases, senescent Aschoff bodies and endomyocardial fibrosis were present in 392 cases of healed rheumatic carditis. In eight cases of active rheumatic carditis, young Aschoff bodies, alteration in the collagen fibers, exudation, and degeneration of myofibers were present. Preoperative study had failed to reveal clinical evidence of activity of rheumatic fever.[317]

Views on the pathogenesis of rheumatic endocarditis may have to be revised. The concept of fibrinoid degeneration and of collagenous vascular disease in general was challenged and displaced. New studies resurrected the hypothesis of thrombosis of von Rokitansky and later of Duguid as a cause. The intravascular substance was identified as an incompletely organized deposit of fibrin by Magarey and by Tweedy. Collagenous degeneration probably has been mistaken for hyaline-like deposits of condensed fibrin derived not from fibroblasts but from fibrinogen of the blood.[318]

Rheumatoid Arthritis.—Infection once seemed to be incriminated as a cause of rheumatoid arthritis, then for a time a metabolic disorder or some endocrinal disturbance. The relation of infection to acute rheumatic fever, to rheumatoid arthritis, and to experimental work on the subject were reviewed by Favour and his associates. Comment in the essay states that "this story

—like a Japanese print without borders—has no conclusion." Much more research is necessary. Current attention is directed largely "to various toxic methods of suppressing the normal immune response of the host," (hormonal therapy). The procedure "has created more problems than it has solved."[319] Question arises whether cortisone ever is indicated for the treatment of rheumatoid arthritis. According to editorial opinion the answer thus far is no.[320] There is no good evidence that cortisone improves the outcome.

A new test, the agglutination of sensitized sheep red cells, was proposed as a diagnostic aid. Unfortunately, it is not always positive in the disease, it has no prognostic value, and it has not aided better understanding of the problem. The reactant seems to be either an antibody to a normal constituent of α-globulin or a component of complement.[321]

The 11th rheumatism review, published in the November and December 1956 issues of the *Annals of Internal Medicine*, covered 2339 papers and books on the subject.

Meningococcal Meningitis.—A study was made of 63 sporadic cases of meningococcal meningitis among recruits over four years. In treatment, penicillin or sulfadiazine or both were used. Meningitis occurred in several patients who had just received penicillin for other reasons. In spite of early adequate treatment, complications occurred in 50%. Six died, four from the Waterhouse-Friderichsen syndrome for which cortisone therapy was ineffective. Evidently, infectious diseases amenable to antimicrobial therapy are by no means always curable or lacking in complications.[322] The death rate still remains high in patients with vascular collapse, despite treatment with antimicrobics, arterenol, and adrenoid corticoids. Five of ten patients died, and all had massive hemorrhage in the adrenal glands.[323] Children who have had meningitis should be observed for many years. Epilepsy, disorders of behavior, deafness, and other sequels occur even after antimicrobic therapy. In one series of cases there was evidence of permanent damage in 22% of patients.[324]

Gonorrhea.—Despite penicillin therapy, the incidence of gonorrhea remains high. Some reasons for this may be as follows: reinfection, inadequate dosage of penicillin, destruction of penicillin by penicillinase, resistance of inactive gonococci, and misdiagnosis.[325] The true incidence of gonorrhea is unknown, and the problem is far from settled.

According to British observers, impetigo is caused by staphylococci, mostly penicillin-resistant and chiefly of phage Type 71, and hemolytic streptococci. Question arose whether both germs may be causes or if one or the other is a secondary invader.[326]

Diseases Caused by Other Microbes

Psittacosis.—After quarantine regulations controlling the interstate shipment of psittacine birds were relaxed in 1951, the incidence of psittacosis increased. In Cleveland, 71% of 24 railway-car workers had serologic evidence of psittacosis, and a number were sick after exposure to parakeets in transit. The infection apparently was conveyed to members of families who had no contact with the birds, since the blood of 14% of them had a high antibody titer. Among 23 persons who had antibody, 7 had severe illness like that described in textbooks as "typical" psittacosis, 4 had mild respiratory tract infection, and 12 recalled no illness.[327] In another report, 5 of 12 family members exposed to parakeets had psittacosis in varying degrees of severity, from an inapparent infection to one that ended fatally.[328] Evidently so-called typical cases are only the severest forms of psittacosis, which like many other diseases has a spectrum of graded severity. Mild cases and inapparent ones usually are unrecognized or misdiagnosed.

Turkeys infected with ornithosis gave rise to 17 cases, mostly in eviscerators in a New Jersey processing plant.[329] Psittacosis (ornithosis) in Texas usually is an occupational disease contracted by those who

handle turkeys. About 200 cases were observed in 1954.[330]

Q-Fever.—An epidemic of Q-fever in Algeria affected all members of two companies of soldiers who had travelled in cattle cars. The symptoms were like those of grip, there was no catarrh, and none were said to have had pulmonary lesions.[331] Pulmonary involvement was not mentioned in the early Australian reports either, but elsewhere it is a prominent feature of the disease. Without roentgenography, pulmonary lesions may pass unnoted.

During 18 months, in the semiarid cattle country of Texas, 31 patients diagnosed as having viral pneumonia were found to have Q-fever. No doubt many more unrecognized cases occur. The febrile period usually lasted about 5 days; after treatment with tetracycline drugs, about 3.6 days. The mortality rate was low, and the efforts of controlling vector ticks seemed to be futile.[332]

Volunteers were infected by inhalation of graded amounts of Coxiella burnetti. The incubation periods ranged from 10 to 17 days, in inverse proportion to the size of the dose. About 40% had clinical illness, one-half of them with pneumonia. About 60% were not sick, but most of these developed complement-fixing bodies indicating inapparent infection. Oxytetracycline administered late in the incubation period prevented clinical disease, but given 24 hours after exposure it did not. The drug caused prompt therapeutic response.[333]

Cat-Scratch Disease.—Eleven cases were reported from Nova Scotia. Diagnosis was made by the history of having been near a cat or having been scratched by one, the clinical course, and histologic changes in tissue from abscesses or lymph nodes. The skin test made in only one patient gave a positive reaction. It may be questioned, in the absence of other specific data, whether many or most of the patients acutally had the disease.[334]

An intradermal test made with specific antigen eight days after a man recovered from cat-scratch fever caused a severe recurrence of disease, lasting a week. Although the pathogen may be one of the Miyagawanella, the complement-fixation test for the psittacosis-lymphogranuloma venereum group of agents gave a negative result. Four months later, the family of cats suspected as the source developed a viral infection of the respiratory tract, and one had pneumonia. No relation to the human disease was established.[335] Symptoms disappeared in six patients after excision of the "major" focus of infection.[336] This is hardly a desirable procedure if other foci are present. In anthrax and bubonic plague excision of lesions was abandoned.

Cat bites may infect man with other pathogens. About 60 cases of infection with Pasteurella multocida have been reported. Another one was observed as an abscess which resisted antimicrobic therapy.[337]

Rickettsia.—The final link in the chain of evidence relating epidemic typhus to Brill's disease as proposed by Zinsser was furnished by the demonstration of R. prowazekii in lymph nodes of healthy persons.[338] A similar finding had been made previously regarding Rocky Mountain spotted fever. It is likely that clinical counterparts to Brill's disease occur in other rickettsioses.[339] The persistence of Rickettsia in healthy persons for years suggests that man is an interepidemic reservoir of infection for typhus and very likely of Rocky Mountain spotted fever, scrub typhus, and others. Arthropods take Rickettsias by feeding on such carriers and thus perpetuate the infection.†

Inoculation of living E strain typhus Rickettsia as a vaccine apparently provided effective immunity for about three years. Reactions occurred, and mild infection occasionally followed.[340] The question raised in the preceding paragraph of persistence of living Rickettsia and on a preceding page of the danger of live poliomyelitis vaccine virus in inoculated persons must be consid-

† Dr. Henrique da Rocha-Lima died in April, 1956, in Brazil.

ered. It is better perhaps to prevent typhus by delousing or defleaing and by other sanitary measures.

Histoplasmosis.—Furcolow classified histoplasmosis clinically into asymptomatic, mild, moderate severe, acute epidemic, and chronic progressive forms. Inapparent or asymptomatic forms far outnumber overt ones. The disease is mistaken easily for colds, viral pneumonia, coccidioidomycosis, and pulmonary tuberculosis.[341] In a sanatorium for tuberculosis, in Missouri, 7% of 600 patients supposedly tuberculous actually had histoplasmosis. On the basis of this percentage, an estimated 1200 patients with wrong diagnoses are in other sanatoriums in areas where the sensitivity of adults to histoplasmin exceeds 50%.[342]

Histoplasmosis, and other fungal infections, have a tendency to be disseminated and severe in patients whose resistance is low owing to some other chronic disease. Histoplasmosis and lymphoma were present in 25 recorded cases.[343,344]

In an epidemic of unknown source among 361 school children in Arkansas, 146 were inapparently infected. Thirty-six clinical cases developed in a five-week period.[345] In New York State, two men got histoplasmosis two weeks after inhaling dust from a decayed tree stump wherein Histoplasma capsulatum was present.[346] The question is whether the organisms thrive in dust naturally or were deposited there by rodent or avian carriers.

Surprisingly few cases of histoplasmosis have been recognized in Panama since it was first discovered there, 50 years ago. In a survey, 39% of natives reacted to the histoplasmin skin test, and it is likely that clinical diagnoses often were missed. Peabody reported a fatal case in a sailor who could have been infected elsewhere. Cortisone therapy probably caused dissemination of the infection.[347]

Mention still is made of the clinical resemblance of histoplasmosis to kala-azar, or leishmaniasis, yet in my experience there is little similarity even in the severest cases. However, diagnostic confusion may occur in unusual ones, as follows: A three-month-old papule excised from the chin of a girl on section contained intracellular bodies resembling H. capsulatum. I doubted this identification because solitary dermal lesions had not been recognized in histoplasmosis. While the case was under study, Symmers' report appeared of solitary cutaneous lesions in two patients.[348] Nevertheless, in mine there was no evidence of histoplasmosis. After learning that the girl had left her residence in Italy a year ago, a diagnosis of oriental sore was made. In tissue stained by Giemsa's method the bodies were those of Leishmania tropica.[349]

Symmers described the first indigenous case of histoplasmosis in England.[350] In this instance its confusion with sarcoidosis arose, as in one of my patients.[351] Histoplasmosis is present in Peru[352] and in Indonesia, where 2.7% of children and 9% to 12% of adults reacted to the histoplasmin skin test.[353] A dog succumbed to generalized histoplasmosis in Ontario. Report of the disease in a bear and in a horse was cited.[354]

In mice that survived inoculation with H. capsulatum the fungus was found in the spleen and liver 45 weeks afterward. There was little difference whether the mice had presumably been immunized or not.[355] By using the mouse inoculation method for the isolation of H. capsulatum, 6% of 193 specimens tested gave positive results, as compared with 2% by direct culture on media.[356]

Sixty papers on histoplasmosis were presented at a conference. Proceedings of the meeting are available through the U. S. Government Printing Office.[357] A history of the development of knowledge of the disease was published.[358]

Coccidioidomycosis.—A clinical description of 100 cases of coccidioidomycosis with historical facts about the disease was published.[359] In a series of 50 cases of chronic coccidioidomycosis, pulmonary cavities were present in 21; nodular densities, in 27, and pleural effusion, fibrosis, and infiltrations, in 2 each. Diagnostic confusion with tuberculosis or neoplasm arose.[360] Fatal coccid-

ioidomycosis occurred in a 3-week-old infant in Chicago. Its mother had had a coccidioidal lesion removed from her foot previously that may have served as the source of infection.[361]

Blastomycosis.—Eighty-six cases of blastomycosis, chiefly in Negro laborers, were studied in Memphis hospitals. The disseminated form occurred in 60%; the cutaneous form, in 27%, and the pulmonary form, in 13%.[362] In Virginia, ossial disease in 25 patients was caused by Blastomyces in 11, Coccidioides immitis and Cryptococcus each in 4, Actinomyces in 3, H. capsulatum in 2, and Nocardia in 1.[363]

Ingestion of Cryptococcus neoformans caused systemic infection in monkeys. Because the fungus may be present on fruit skins and in milk, infection in man may arise from these sources.[364] Man is susceptible to all the ringworm funguses which attack animals except Microsporum audouini. A large part of ringworm infection in man is derived from sources in infected animals.[365] Ajello discussed soil as the reservoir for a number of pathogenic funguses, especially H. capsulatum, C. immitis, Aspergillus, Candida, Cryptococcus, Allescheria, Trichophyton, and others.[366]

Leptospirosis.—In Georgia, after 55 persons bathed in a dammed creek used by farm animals, 25 came down with nonicteric leptospirosis. Cattle, swine, and dogs in the vicinity were infected, as indicated by the results of serologic tests.[367] The infection is widespread in North Carolina, where all samples of blood sent to the state laboratory are tested routinely for evidence of leptospirosis. Specific antibody was present in 109 of 441 specimens. The disease often was mistaken for viral hepatitis or unrecognized, and many patients were anicteric.[368] Three patients in Alabama had canicola fever with meningitis. Diagnosis was made by an increase in the specific antibody titer and the presence of the Leptospira in household dogs.[369]

Leptospirosis accounted for 35% of 852 febrile patients in Malaya. Dengue, typhus, and malaria were next in order of frequency, and in 30% of cases no diagnosis was established. Leptospirosis was a relatively mild disease, with jaundice in 7% of cases and only two deaths. Penicillin, chloramphenicol, and oxytetracycline had no beneficial effect. Leptospiremia was present in 59%, and 13 serotypes of Leptospira were isolated.[370]

In general, the pomona, mitis, grippotyphosa and hebdomadis varieties of Leptospira caused mild or subclinical infection, while L. icterohaemorrhagiae, australis A, and bataviae caused severe hemorrhagic disease. The hemolytic activity of the latter group may account for its greater pathogenicity.[371]

Syphilis.—Although modern therapy reduced the death rate from syphilis from 8.4 to 3 per 100,000 in 10 years, an estimated 2,000,000 persons in the United States need treatment, and more than 85,000 new infections occur annually. Unless better methods of control are applied, the prospect of eradicating syphilis is dim.[372] Between 1940 and 1946 about 500,000 members of the armed forces had syphilis. Based on this figure, about 15,000, or 3%, probably have neurosyphilis now. The average cost of maintaining a paretic patient is $40,000.[373] By tracing persons who had been exposed to two syphilitic patients, two epidemiologic chains were discovered, involving 25 new early infections. In North Carolina, 50 early cases a month are being reported.[374]

According to Laird, congenital syphilis is not prevented as often as it should be. Reasons for failure are the absence of antenatal observation, failure to apply serologic tests for syphilis, late diagnosis, premature labor, refusal of treatment, and falsely negative tests.[375]

Opinion in some quarters casts doubt on the value of specific therapy. Benvenuto Cellini had syphilis at the age of 25, but had an unusually active, useful life and died at the age of 71 from another disease.[376] From the observations of Boeck, in Oslo, 50 years ago, it appeared that patients treated with medication then in use fared no better than

untreated ones. A retrospective study was made of Boeck's untreated patients in 1955. Between 60% and 70% had gone through life with little or no inconvenience, yet 24% had secondary lesions, 90% had a recurrence during the first year, and 20% had subsequent recurrences. Such victims are dangerous sources of infection. In Moore's series of patients under modern management, 9.5% had an early relapse, and Merrell reported only 2%.[377] The current status of treatment was reviewed by Thomas.[378]

A newly devised Treponema pallidum immune adherence (TPIA) test was said to be simpler and cheaper to do but as reliable as the immobilization (TPI) test for the diagnosis of syphilis.[379]

Trypanosomiasis, like syphilis, may cause degeneration of the fibrillar system of the central nervous system resembling that of a heredodegenerative disease. The adiposogenital syndrome and cryptorchism developed in a victim.[380] Knowledge of American trypanosomiasis, Chagas' disease, was reviewed with special reference to the characteristic involvement of the myocardium.[381]

Schistosoma mansoni worms survived for long periods and grew in length in nutrient medium in test tubes.[382] The subject of schistosomiasis was reviewed by Diaz-Rivera.[383]

Toxoplasmosis.—Toxoplasmosis seems to be widespread. Infection usually is inapparent, and only rare overt cases come to medical attention. Surveys made by applying skin tests or serologic tests indicated infection in from 30% to 70% of persons between the ages of 40 and 60 years. Evidence incriminated undercooked pork as an important source. If this be the case, the epidemiology of toxoplasmosis resembles that of trichinosis.[384] A laboratory worker whose blood had no specific antigen accidentally sprayed toxoplasma on his face. Two months later he had an episode of chills, fever, vomiting, and a rash. A diagnosis of toxoplasmosis was made on the basis of a positive dye test and complement fixation.[385] The properdin system seemed to be necessary in order for specific antibody to exert its adverse effect on Toxoplasma.[386]

Amebiasis.—According to an analysis of 148 fatal cases of amebiasis, little progress has been made in lowering the death rate. Correct diagnosis had been made in only one-third of the cases. Deaths occurred chiefly among older men. The progression of the disease often was rapid, and most fatalities occurred within six months. The chief causes of death were perforation of the bowel and peritonitis, uncomplicated dysentery, and hepatic and pulmonary abscesses. Hepatic abscess was present in 61%.[387] The current methods of therapy were outlined.[388]

Volunteers were given amebacidal drugs before inoculation with Endamoeba histolytica. Glycobiarsol (Milibis) and diiodohydroxyquin (Diodoquin), in one-third to one-sixth of the curative doses, prevented infection; quinacrine (Atabrine) and chloroquine did not.[389]

Leishmaniasis.—Eleven cases of cutaneous leishmaniasis were observed in Panama. The infection often was not confined to the papule. Beady nodules in the skin nearby contained many Leishmania bodies, but with little inflammatory reaction. Enlarged regional lymph nodes were not examined. Stibophen (Fuadin) was helpful in therapy.[390] Apparently both cutaneous and mucocutaneous leishmaniasis, or espundia, occur in Panama. L. tropica and L. braziliensis, the respective causes, are the same morphologically, but when the mucous membrane is involved in addition to the skin, the diseases are differentiated clinically. Report was made elsewhere in this review of a case of imported cutaneous leishmaniasis, at first mistaken for histoplasmosis.[349]

Trichinosis.—Substitution of grain for raw garbage in feeding hogs reduced the incidence of trichinosis in pork to about 0.05%. To account for the perpetuation of the disease in grain-fed animals, the possibility of infection from ingesting flesh of infected wild animals was considered. In Iowa, foxes, minks, coyotes, raccoons, and opossums have trichinosis. Its existence in

so many animals makes eradication almost impossible.[391]

Echinococcosis was observed in 180 Amerinds and Eskimos in northwestern Canada, where the infection is endemic. In one series, of 35 patients, 29 had pulmonary cysts and 6 had hepatic cysts.[392]

In a world-wide survey of malaria, Russell pointed to its rapid retreat since 1880, when its range extended from Canada and Siberia to Argentina and Madagascar. At present, its northern limit in this country is at the Rio Grande River. It was estimated that there are now over 200,000,000 persons with malaria and 2,000,000 deaths from it annually.[393] In the United States more than 137,000 cases were reported in 1935 and 477 in 1955. A number of the latter were imported in military personnel returned from endemic areas.[394]

Miscellaneous Topics

Cortisone Therapy.—During cortisone therapy a patient with leukemia was afflicted with herpes simplex, against which she was vaccinated with antismallpox virus. A few days later fatal generalized vaccinia flared. Cortisone apparently increased susceptibility to the virus.[395] Cortisone depresses the defences of the body against infection by inhibiting the phagocytic activity of the reticuloendothelial system and lowering the number of leukocytes and the amount of γ-globulin. Its beneficial action in a few infections depends on suppression of an inflammatory reaction.[396]

By using a transparent chamber inserted into rabbits' ears, Zweifach observed the early cellular response to injury. Leukocytes first adhered to the capillary endothelium, then by active motility emigrated in a random manner. A gelatinous precipitate formed near the site of injury. The administration of cortisone inhibited the adhesion of leukocytes, their emigration, and their accumulation in tissue spaces, probably by a direct action on the endothelial cells and leukocytes.[397]

Resistance to Infection.—Various nonspecific physiologic and biochemical disturbances influence resistance to infection. They are independent of specific immune factors and account for many otherwise unexplained irregularities of resistance or susceptibility. The changes may occur rapidly and are reversible. For example, mice given injections of toxins and inoculations of virulent bacteria were harmed more than unpoisoned mice. When infection was induced at a later time, mice which had been treated with toxins were less affected than untreated ones. The observations were consistent with Almoth Wright's concept of a "negative phase of resistance" after vaccination. A short period of fasting increased susceptibility, but normal resistance rapidly returned when a normal diet was fed. Even on a deficient diet, resistance was reestablished, but more slowly, in underweight animals.[398,399]

The injection of lipopolysaccharides or endotoxins of various bacteria stimulated nonspecific resistance to infection. There also was increased resistance in mice after the injection of properdin.[400] Treatment of mice with chlorpromazine and phenoxybenzamine (Dibenzyline) seemed to protect them from the toxins of Escherichia coli, Salmonella typhosa, Shigella dysenteriae and other bacilli, but increased the mortality rate from poisoning with the toxins of Clostridium perfringens.[401] Similar nonspecific resistance to endotoxins was reported by others.[402]

New studies on nonspecific mechanisms of defense against infection were reviewed briefly. Properdin, a euglobulin, together with complement and magnesium ions seems to play an important role. Effort is under way to prepare properdin for therapeutic use. Beta-globulin, alpha$_1$-globulin, lysozyme, and phagocytin also seemed to play a role in defense against infection.[403]

Long discussed the complex interrelationship of infection, nutrition, endocrinal disturbances, and allergy.[404] Lawrence reviewed the important but poorly understood field of delayed allergic inflammatory responses.[405] This phenomenon in its typical form is acquired after infection with bac-

teria, viruses, fungi, and spirochetes. It is most obvious in tuberculosis, brucellosis, tularemia, glanders, chancroid, and trichinosis. In streptococcal infection the matter pertaining to rheumatic fever is unsettled. Delayed allergic reactions no doubt play a role in the immunologic and clinical behavior of many infectious diseases.

A patient with acquired hypogammaglobulinemia had a normal mechanism of host resistance to infections except for an abnormal synthesis of gamma-globulin. Repeated bacterial infections were controlled by therapy with sulfadiazine and gammaglobulin. Patients with hypogammaglobulinemia apparently are able to combat viral infections better than bacterial ones.[406]

Other Topics.—The Westergren method of measuring the sedimentation rate of red cells is the simplest one to indicate the presence of inflammation. Similar information yielded by the C-reactive protein test provides additional information in the earliest stages of disease. There are more than 30 known changes in blood associated with inflammation.[407]

Oral and rectal clinical thermometers presumably sterilized by immersion in antiseptic solutions were found to harbor staphylococci, hemolytic streptococci, and other bacteria. Cleaning with soapy cotton and immersion in 70% isopropyl alcohol containing quaternary ammonia compounds and iodine was recommended.[408]

By examining gauze pads suspended for 24 to 48 hours in flowing, treated sewage, numerous pathogenic microbes were recovered which would have been missed by the usual methods of sampling. Coxsackie and poliomyelitis viruses, Salmonella typhosa and Mycobacterium tuberculosis were present. Many of the tubercle bacilli were resistant to isoniazid.[409]

A study was made of epidemiologic problems in the Arctic. Tuberculosis, pneumonia, meningitis, colds, typhoid, bacillary dysentery, smallpox, measles, trichinosis, rabies, diphyllobothriasis, and other infections occur.[410]

Use of Microbes in Warfare.—Wedum outlined the complexities of defense against the possible use of microbes by an enemy at war. It would be impracticable to immunize a population specifically in anticipation of an attack with any one of the numerous pathogens likely to be used. Should it be attempted, quick identification of the microbe, isolation of the victims, and proper therapy would be in order.[411] An efficient diagnostic laboratory was designed.[412]

Small groups of persons, no doubt, could be infected or poisoned by planned intent. It is comforting to feel that an attempt to induce an extensive epidemic artificially has only the smallest chance of success. The coincidence of many factors is essential. I would find difficulty in choosing an appropriate pathogen. Perhaps there are some, but it is hoped not. Matters would be different, of course, if nuclear warfare forced the evacuation of cities. Overcrowding, discomfort, lack of food and sanitation in reception centers provide suitable conditions for an epidemic.[413] Most ominous, perhaps, is the possibility of developing new viruses artificially.[414] Few things might have greater consequences to humanity than the evolution of a "new" virus with the spreading power of influenza and the virulence of smallpox, against which no one at present is immune.[415]

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Case Reports

Thalamic Syndrome Due to Cerebral Embolism in Rheumatic Heart Disease

Successful Treatment with Cortisone

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Since the pioneer work of Head and Holmes,[1] the physiological and psychological aspects of central pain have been the subject of many studies. Central pain is of specific character: It is severe, it is of burning quality, it affects the whole personality and may cause changes in behavior, it is aggravated by emotional influences and sensory stimuli, and it is generally not alleviated by the usual analgetics. Frequently the pain does not leave the patient during the night and may be so severe as to lead to suicide. At times it is accompanied by vasomotor and trophic disturbances.

In spite of numerous clinical and experimental investigations, complete understanding of the problem of central pain has not yet been achieved. Since the work of Dejerine and Roussy,[2] the thalamus and its cerebral connections are held responsible for the central pain sensation.

The mechanism by which damage to the thalamus causes this specific pain is badly understood. It has been explained by an irritative effect of the thalamic lesions,[1] by "release" from cortical inhibition due to interruption of corticothalamic connections,[3] and, more recently, by a "disturbance of the normal pattern of the thalamocortical connections,"[4] the arrival of the abnormal pattern of excitation in the frontal lobes provoking the abnormally exaggerated affective attitude of the patient.

In some cases of hemiplegia, central pain forms the chief complaint, and in such cases the damage is considered to be in the thalamic-cerebral connections.[5] In these patients the pain is perceived in the paralyzed half of the body and usually involves the distal parts of the limbs more than the proximal. Cases in which central pain is restricted to one extremity or to a part of it or to the face have been described, but are rare.[6,7]

The present case of central pain seems of interest because of the restriction of the pain to a sharply limited part of the body (the fingers of one hand), because of its rare etiology (cerebral embolism in rheumatic valvular heart disease), and because of the striking therapeutic effect of cortisone.

Report of Case

A 46-year-old housewife, mother of two healthy children, was admitted to the medical department on July 26, 1955, complaining chiefly of pain in the fingers of the left hand. As a child she had rheumatic fever with polyarthritis, and at the age of 16 a heart lesion was diagnosed. Since the age of 21 she suffered from shortness of breath and was treated periodically with digitalis, during the last few months with 0.25 mg. of digoxin per day. Her legs had never been swollen. In 1948 a third pregnancy was interrupted in the second month because of her heart condition. For the past eight years she occasionally noticed slight swelling of the left arm after sleeping on her left side. Six weeks previous to admission she woke up one morning with a slight disturbance in speech, which lasted for a few minutes

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only. At the same time she felt a sharp pain in the tip of the tongue and in all fingers of the left hand, with slight weakness of the left arm. After a short time the pain concentrated in the thumb and the index and middle fingers of the left hand, where it has since persisted. The pain was burning and severe and sometimes prevented her from falling asleep. Often she could not bear the slightest touch to the three fingers, and because of the pain she could not take any object in her left hand. The three fingers were kept in slight flexion, as in this position the pain was most bearable. For the past three weeks she had noticed that the nails of these three fingers did not grow and the color of the thumb and the index finger became bluish white. Physical examination revealed the patient to be in fair general condition, without dyspnea, cyanosis, or edema. The temperature was normal, the pulse regular, 80 per minute. The retinal fields were normal. She had a mitral flush; the neck veins were not swollen. There were no abnormal findings over the lungs. On percussion the heart was found to be slightly enlarged to the left. A presystolic thrill was felt, and a Grade 2 systolic murmur, a prolonged diastolic murmur, and an opening snap were heard over the apex. The second pulmonary sound was accentuated, and a systolic and a soft blowing diastolic murmur were heard in the second right intercostal space. The liver, felt 2 cm. below the right costal margin, was not tender. The spleen was not palpable. Examination of the upper extremities showed the left thumb and index finger to be slightly bluish, with a glossy skin, which was also present over the left middle finger. The three fingers were kept in slight flexion and were extremely sensitive to touch. The interossei muscles were slightly atrophic. There was no edema. Both radial pulses were equal and of good amplitude, and the blood pressure was 150/90 in both arms. The ulnar pulses of both hands were felt weakly, and a test described by Allen et al.[8] revealed a deficiency of flow in both ulnar arteries. On hyperabduction of the arms the radial pulses did not disappear. The Adson[9] test for scalenus anticus syndrome was negative on both sides. The cubital venous pressures were normal and equal. There was no edema of the lower extremities, and pulsations in both arteriae dorsales pedes were felt.

Neurological Examination.—The pupils were equal and reacted to light and convergence. There were no sensory changes in the face. A slight central weakness of the left facial nerve was noted. Tongue protrusion and other movements were free; swallowing was normal. There was slight weakness of the left arm, but the patient was able to perform all requested movements. The left biceps reflex was slightly increased. The thumb, the index finger, and the middle finger were kept in slight flexion, but the patient was able to stretch them, although this movement provoked pain. There were marked sensory changes in these three fingers: extreme sensitiveness to touch, pressure, and pin prick and, especially, to cold and heat. The sensation caused by touch and prick was said to have a peculiar character, being less intensive than in the right hand but accompanied by a general unpleasant feeling. Vibration and position sense in the upper extremities were not disturbed. No ataxia and no astereognosis were found. The abdominal reflexes were equal. The left patella reflex was increased, and the Achilles reflexes were equal. No Babinski or other pyramidal signs were found; the left plantar reflex was absent. No sensory changes were detected in the lower extremities. The gait was normal, except for the left arm being kept in juxtaposition to the body.

Routine laboratory examinations of the urine and blood were normal; the sedimentation rate was (Westergren) 15 mm. in 60 minutes.

X-rays of the skull revealed hyperostosis frontalis interna with calcification in the falx cerebri; otherwise normal. In the cervical spine there were small anterior osteophytes between the sixth and seventh levels, without narrowing of the intervertebral space and without limitation of movement. There were no cervical ribs. Examination of the heart showed slight enlargement of the left ventricle, marked dilatation of the left auricle, and marked bulging of the pulmonary conus. Both hili were enlarged. X-ray of the hands was normal. Phlebography by separate injection through the left cephalic and basilic veins showed normal patency to the entry of the subclavian vein into the anonyma. No pathologic collaterals were demonstrated. The veins appeared normal.

The electrocardiogram showed left axis deviation, a broad and high P wave, and slight descent of the ST segment in V_4, V_5, and V_6.

Course and Treatment.—During the first four weeks of her stay in the hospital the patient suffered from continuous pain in the fingers of the left hand and required increasing amounts of sedatives and analgetics and finally narcotics. The pain became so severe that she could not sleep and even mentioned suicide as a way out.

The syndrome in the left upper extremity seemed to be due to a central disturbance, which developed at the same time as the slight left hemiplegia. The similarity of the symptoms in the left upper extremity—burning pain, sensitivity to touch, change in color and glossy skin, changes in the nails and atrophy of muscles—with those observed after peripheral nerve lesions, after myocardial infarction, and associated with tumors in the chest, then classified with reflex sympathetic

dystrophy, led us to try cortisone therapy, which has proven effective in some of these cases.[10]

Oral cortisone, 300 mg. per day, was commenced on Aug. 28, 1955. The effect was striking. Within 48 hours the pain had markedly decreased in intensity and after 5 days had disappeared. The patient was discharged from the hospital on Sept. 2, 1955, on a maintenance (100 mg.) dose of cortisone. When she stopped the treatment 10 days later, slight pain in the fingers recurred, to disappear again when cortisone treatment was resumed. When she again discontinued the treatment three weeks later, the pain did not recur. In the meantime the nails had started to grow, and reexamination after 3, 6, and 10 months revealed the patient to be in good condition, without pain and with normal appearance of the skin and nails of the left hand. The slight central weakness of the left facial nerve persisted, and the left biceps reflex was still slightly increased.

Comment

The syndrome presented consisted of slight left hemiparesis with pyramidal signs, severe spontaneous pain with exaggerated pain reaction to various stimuli, diminished cutaneous sensitivity, and vasomotor and trophic disturbances localized in the fingers of the left hand. The pain in the fingers of the left hand appeared simultaneously with pain in the tip of the tongue and the left hemiparesis. The sensory, vasomotor, and trophic disturbances in the fingers of the left hand persisted, while the pain in the tongue disappeared rapidly, and the motor disturbances declined gradually in intensity. These sensory disturbances, severe spontaneous pain with diminished cutaneous sensibility but exaggerated pain reaction of specific quality, that is, hyperpathia or dysesthesia,[11] are typical of a lesion in the thalamus or of its cortical connections.

Although our knowledge of the thalamus is incomplete, its dominating role in determining the quality of sensory perception is generally accepted. It is known that all sensory impulses, except for smell, before reaching the cerebral cortex pass through the thalamus, which may be considered a central synapse. The thalamus is composed of various nuclei, which in respect to their sensory function are connected with specific areas of the cerebral cortex.[12] No doubt there exists a well-defined thalamocortical projection. On the other hand, circumscribed damage to the cerebral cortex results in localized structural change in the thalamus.[12] However, not all thalamic nuclei have their projection in the cortex. The phylogenetically young nuclei are connected with the cortex, while the phylogenetically older are linked with the hypothalamus or with the extrapyramidal system.

The association of the hyperpathia, localized in the fingers of the left hand, with short lasting pain in the tip of the tongue and left hemiparesis, in the absence of evidence of a peripheral nerve lesion or peripheral vascular occlusion, led to the assumption of a thalamic lesion as the cause of the severe sensory disturbances. Because of the sudden appearance of the syndrome in this patient with rheumatic mitral valvular heart disease, it is probable that the thalamic lesion was caused by an embolus.

Thalamic syndrome following acute vascular cerebral events, such as occlusion or rupture of the posterior cerebral artery or of one of the thalamogeniculate branches, are not uncommon and produce the thalamic syndrome of Dejerine and Roussy.[13] In this condition there is hyperaffectivity with a raised sensory threshold—anesthesia dolorosa—in the opposite half of the body, involving the limbs and trunk and sometimes associated with transient or permanent hemiparesis and disturbed deep sensibility.

The syndrome in the present case is of special interest because of the circumscribed localization of the sensory disturbances in the fingers of the left hand. Such sharply delimited localization may be understood in the light of knowledge of the somatotopic arrangement in the the thalamic nuclei, especially the nucleus ventralis posterior. The nucleus ventralis posterior has several subdivisions, among which are the nucleus ventralis posterolateralis and the nucleus ventralis posteromedialis or nucleus arcuatus. Most of the fibers of the spinothalamic tract and of the medial lemniscus end in the nucleus ventralis posterior.[14] While the

somatotopic projection of the distal sensory tracts from the lower extremities is in the lateral part of the nucleus ventralis posterior, those from the hands and the trunk are projected more medially and those from the face most medially.[15]

In the case described by Strauss[7] there were sensory disturbances around the mouth and in one hand: the cheirooral syndrome. In this patient a small tuberculoma was found in the nucleus ventralis posterior of the thalamus at post mortem examination. Garcin and Lepresle[6] described a 65-year-old diabetic who suddenly developed a thalamic syndrome with cheirooral topography and in whom at autopsy a circumscript malacic focus was found in the nucleus ventralis posterolateralis and the most lateral part of the nucleus ventralis posteromedialis of the right thalamus.

The occurrence of such sharply localized thalamic lesions may be explained by the blood supply of the thalamus. Foix and Hillemand[16] described five small branches of the arteria thalamogeniculata, and according to Garcin and Lapresle[6] occlusion of one of these branches may cause sharply circumscribed sensory changes.

The assumption in our case of an embolus in one of the small branches of the arteria thalamogeniculata, supplying the nucleus ventralis posteromedialis, would fit in with the clinical picture and the knowledge of the anatomy of the blood supply of the thalamus.

The striking effect of cortisone on the hyperpathia and the vasomotor and trophic changes of the hand in the present case is not understood. In this respect our lack of knowledge of the action of this drug applies equally to cases of sympathetic reflex dystrophy (causalgia, shoulder-hand syndrome) in which cortisone administration abolished the pain and the trophic disturbances.[10] That the effect of cortisone was not solely due to its euphoric action was demonstrated by objective emprovement in the vasomotor and trophic changes.

Summary

A case report is presented of central pain associated with vasomotor and trophic disturbances in the fingers of the left hand due to cerebral embolism in rheumatic heart disease. The restriction of the pain to a sharply delimited area of the body suggests damage in a circumscript part of the thalamus. The pain and the vasomotor and trophic changes responded strikingly to the administration of cortisone.

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Correction

Dr. Jerome Rötstein has requested that the following correction be made in the article "Steroid Pseudorheumatism," by him and Dr. Robert A. Good, in the April issue of the ARCHIVES:

All sedimentation rates reported in this article were determined by the Westergren method.

Thrombocytopenia and Renal Lesions Associated with Acetazoleamide (Diamox) Therapy

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Recently both thrombocytopenia and renal lesions similar to those produced by sulfonamides have been reported in association with the use of acetazoleamide (Diamox),[1,2] a carbonic anhydrase inhibitor of sulfonamide origin used as a diuretic. Both types of reaction occurred in the following case.

Report of Case

A 61-year-old white man was admitted to the Veterans Administration Hospital, Philadelphia, on March 5, 1956, with a history of recurrent peripheral edema of nine months' duration. One month before admission the edema became persistent and progressive. There were no cardiac or pulmonary complaints, and review of symptoms by systems was essentially negative. Except for edema of the legs, scrotum, and presacral region, the physical examination was within normal limits. The blood pressure was 130/70. Study of the urine disclosed a specific gravity fixed at 1.010. There was marked proteinuria, and the urinary sediment contained occasional casts, red blood cells, and white blood cells. The hemoglobin was 11.4 gm. per 100 ml., and the hematocrit, 36%. The white blood cell count was normal. Serum proteins were 3.5 gm. per 100 ml., of which 1.1 gm. was albumin, and the serum cholesterol was 360 mg. per 100 ml. Venous pressure and circulation time, electrocardiograms, and roentgenogram of the chest were within normal limits.

The diagnosis of nephrotic stage of chronic glomerulonephritis was made, and the patient was started on a program of salt restriction and bed rest. This was supplemented by 2 cc. of an intramuscular mercurial diuretic (meralluride [Mercuhydrin]) daily for four days. There was no diuretic response, and on March 12, 1956, the ninth day of hospitalization, therapy with acetazoleamide was begun. The patient received 500 mg. daily for three days and 250 mg. daily thereafter for six more days. There was improvement in his edema, and his only complaints during this period were referable to a painful discolored right great toe thought to be secondary to arterial insufficiency. Other medications at this time included oral papaverine, 0.2 gm. four times daily, and occasional 30 mg. doses of codeine sulfate. On March 21, 1956, his 17th hospital day and 9th day of acetazoleamide therapy, the patient developed profuse epistaxis followed by generalized ecchymoses, hematuria, and melena. All medications were immediately discontinued. Hematologic studies revealed a platelet count of 18,000 per cubic millimeter, a strongly positive capillary fragility test, and no clot retraction in 24 hours. Bleeding time, clotting time, and prothrombin time were normal. Bone marrow examination was interpreted as showing a normal number of megakaryocytes but no evidence of platelet formation. Platelet-free plasma from the patient agglutinated the platelets in normal platelet-rich plasma in the presence of acetazoleamide. Platelet agglutination did not occur in the absence of acetazoleamide or when normal plasma was substituted for the patient's plasma.

The patient's course was stormy, and multiple transfusions were required to combat the anemia secondary to hemorrhage. There was a progressive rise in the blood urea nitrogen to a level of 160 mg. per 100 ml. Clinical and laboratory data are shown in Figure 1. Cortisone and corticotropin were administered, but, because of increasing edema, they were discontinued. On March 28, 1956, no platelets were present on direct count or noted on blood smears. Subsequently, there was a gradual increase in the platelet count to normal. At a level of 30,000 per cubic millimeter, bleeding ceased, and thereafter there was progressive improvement in the patient's clinical picture. The blood urea nitrogen dropped to 35 mg/100 ml. Clot retraction time and capillary fragility tests returned to normal. Trials with meralluride and papaverine, the other medications the patient had received, did not result in thrombocytopenia.

The patient's nephrotic syndrome responded well to intravenous salt-poor albumin, and therapeutic efforts were directed chiefly toward his peripheral arterial insufficiency. On May 28, 1956, signs and

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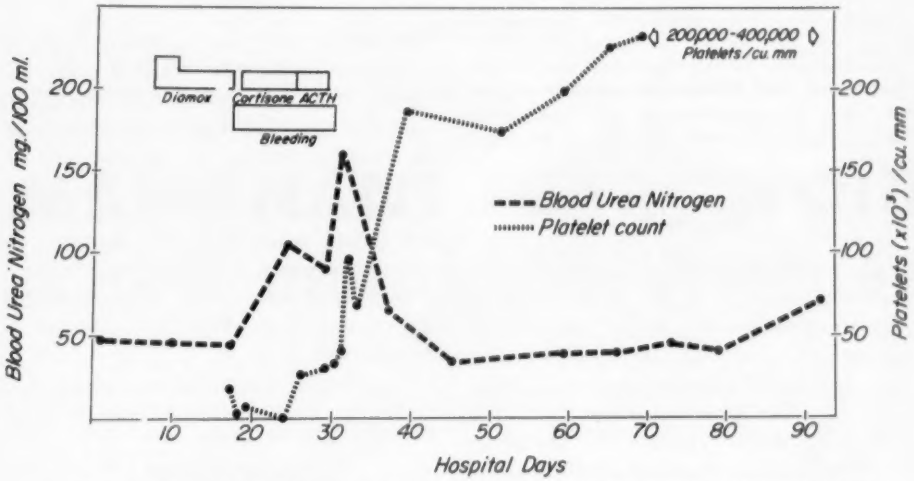

Fig. 1.—Clinical and laboratory data in patient with thrombocytopenia and renal lesions associated with acetazoleamide therapy.

symptoms of acute thrombophlebitis developed in the right leg, and anticoagulant therapy was instituted. On June 2 the patient developed pain in the left side of the chest accompanied by hemoptysis, cyanosis, dyspnea, and tachycardia. Chest roentgenogram confirmed the clinical impression of pulmonary infarction. Oxygen and antibiotics were added to the therapeutic regimen, but the patient's course was rapidly downhill, and he died on June 7, 1956.

At necropsy * a fresh pulmonary infarct was present in the left lower lobe. There were organizing thrombi in the right iliac vein and both renal veins. The right kidney weighed 135 gm., and the left, 130 gm. The cortical surfaces were yellowish-tan and granular, and the renal capsules were removed with difficulty. On cut section obliteration of the anatomical markings of the kidney parenchyma was noted. Microscopically a diffuse membranous glomerulitis was present. The renal tubules were dilated and contained casts and birefractive crystals (Fig. 2). The crystals resembled those obtained by recrystalizing acetazoleamide in an acid medium. There was evidence of tubular epithelial degeneration and regeneration. A marked renal interstitial inflammatory reaction was present, and there was fibrinoid

* Performed by Dr. A. L. Pietroluongo.

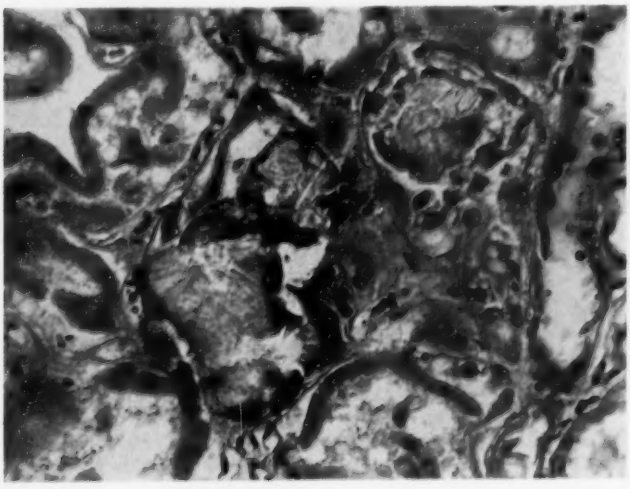

Fig. 2.—Photomicrograph of kidney, showing presence of crystals resembling acetazoleamide in renal tubules; × 250.

necrosis of many arterioles. The final pathological diagnosis was chronic membranous glomerulonephritis with superimposed changes of sulfonamide (acetazoleamide) toxicity, right iliac vein and bilateral renal vein thromboses, pulmonary infarction and bronchopneumonia, and generalized atherosclerosis with early gangrene of the right toe.

Comment

The clinical picture and the presence of plasma antibodies capable of agglutinating platelets in the presence of acetazoleamide is evidence that this drug was responsible for the patient's thrombocytopenic purpura. Acetazoleamide is a sulfonamide, one of a group of drugs capable of producing thrombocytopenia.[3] Recently agranulocytosis has been reported following its use.[4] This case and the mechanism involved closely resembles those in which thrombocytopenia was produced by allylisopropylacetylcarbamide (Sedormid), quinidine, and quinine. This has been the subject of recent excellent reviews by Ackroyd[5] and Bolton.[6] In the case of thrombocytopenic purpura associated with acetazoleamide reported by Reisner and Morgan,[1] a platelet lysin appears to have been responsible for the thrombocytopenia. In their case, acetazoleamide had been administered for three weeks before the onset of symptoms, and the rate of recovery of the platelet count was slower than in the present case.

At necropsy, in addition to the microscopic lesions of glomerulonephritis, crystals resembling those of acetazoleamide were present in the tubules, and there were marked interstitial inflammatory changes and fibrinoid necrosis of arterioles, changes that have been attributed to sulfonamide toxicity.[7]

Summary

A patient with the nephrotic stage of glomerulonephritis who received acetazoleamide (Diamox) developed thrombocytopenic purpura. Plasma antibodies capable of agglutinating platelets in the presence of acetazoleamide were present. The patient recovered from his thrombocytopenia but died approximately 10 weeks later. Microscopic examination of the kidneys disclosed chronic glomerulonephritis and renal lesions suggestive of those produced by antibacterial sulfonamides.

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ALBERT SJOERDSMA, M.D., Ph.D.; LUTHER L. TERRY, M.D., and SIDNEY UDENFRIEND, Ph.D., Bethesda, Md.

MALIGNANT CARCINOID
a new metabolic disorder

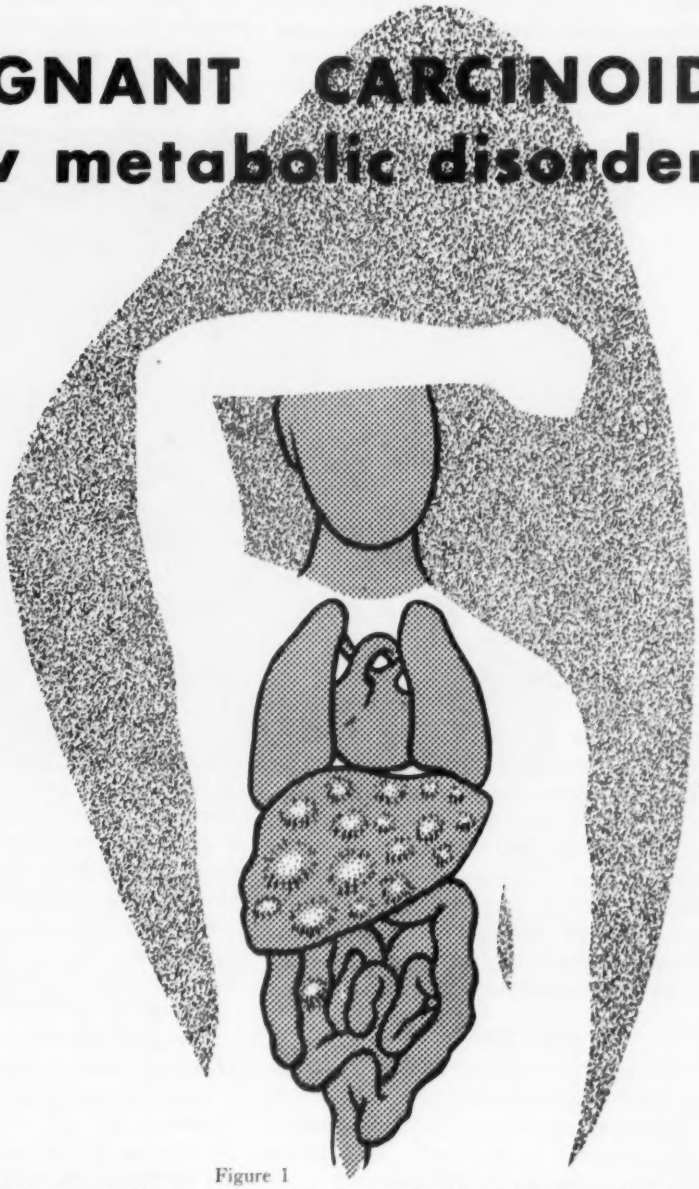

Figure 1

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From the Clinic of General Medicine and Experimental Therapeutics and Laboratory of Clinical Biochemistry National Heart Institute.

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Introduction

Carcinoid is a relatively benign tumor of the gastrointestinal tract and is thought to originate from the chromaffin cells in the mucosa. Although most commonly located in the appendix, carcinoids have been found from the cardia of the stomach to the rectum. Occasionally these tumors become more malignant and invade adjacent tissues and metastasize to the liver and other distant organs. Histologically no differentiation can be made between the small, apparently benign lesion and the distant metastatic tumors. Thus, many workers feel that all carcinoid lesions are potentially malignant.

Although most carcinoids are discovered incidentally at the time of surgery or autopsy, it is now apparent that some carcinoids produce a variety of clinical manifestations through secretion of the pharmacologically active agent, serotonin (5-hydroxytryptamine).

Clinical Manifestations

Recently an unusual clinical syndrome has been described which is associated with "malignant" carcinoid of the small intestine and metastasis to the liver. The principal manifestations are as follows:

1. Vasomotor disturbances—cutaneous flushes and "cyanosis"
2. Hepatomegaly—large, nodular liver
3. Intestinal hypermotility—cramps, diarrhea, vomiting
4. Bronchoconstriction—cough, dyspnea, wheezing
5. Cardiac involvement—endocardial fibrosis with valvular deformity
6. Absence of hypertension—incidence no greater than general population
7. Prolonged clinical course—patients survive years longer than those with other tumors with metastasis

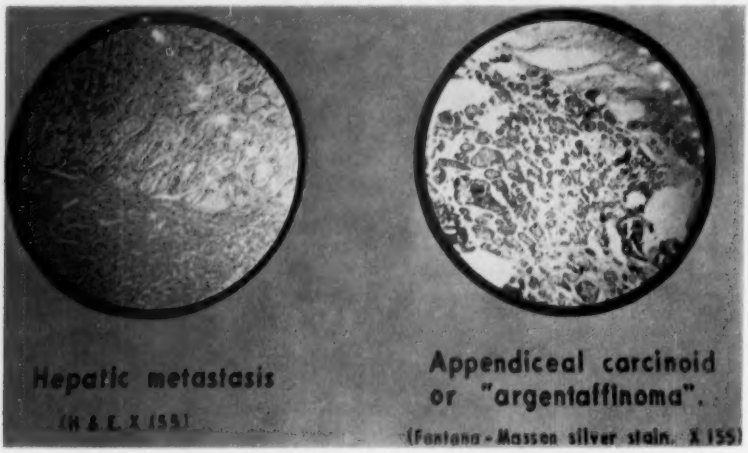


Fig. 2.—Photomicrographs of hepatic metastasis and appendiceal carcinoid.

The Metabolic Disorder

Recent studies have revealed that most of the manifestations of the carcinoid syndrome can be attributed to the secretion of serotonin (5-hydroxytryptamine) by the tumor cells. Studies in experimental animals indicated that serotonin is derived from the amino acid tryptophan and is metabolized by oxidative deamination to 5-hydroxyindoleacetic acid (5-HIAA).

Biogenesis and Metabolism of Serotonin. The 5-hydroxyindole pathway of tryptophan metabolism is shown in Figure 4.

Chemical studies of carcinoid tissue have shown a high level of serotonin as well as the presence of enzymes which are required for the formation and oxidation of serotonin (Table 1).

In addition, study of carcinoid patients revealed an elevated level of serotonin in

Fig. 3.—Patient showing typical flushing and persistent "cyanosis."

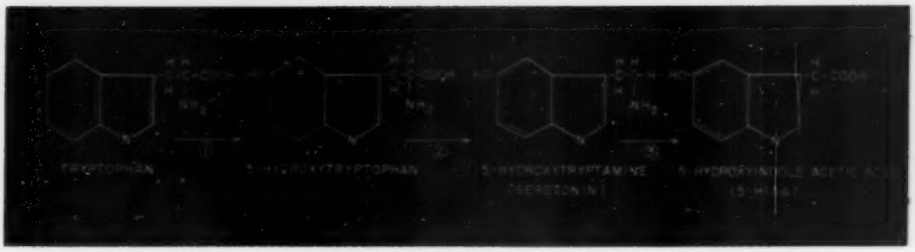


Fig. 4.—Chemical pathway.

the blood and an increased excretion in the urine of its metabolite, 5-HIAA (Table 2).

Proof of the precursor relationship of tryptophan to serotonin in man was shown by the fact that lowering and raising the dietary intake of tryptophan resulted in a corresponding variation in the urinary excretion of 5-HIAA (Fig. 5).

TABLE 1.—*Chemical Studies on a Carcinoid Tumor*

Total 5-hydroxyindoles	1.2mg./gm.
Serotonin	0.8mg./gm.
Enzyme No. 1 (tryptophan oxidase)	?
Enzyme No. 2 (5-OH-tryptophan decarboxylase)	Present
Enzyme No. 3 (serotonin oxidase)	Present

Diagnosis

On the basis of this understanding of the underlying chemical characteristics of the syndrome, a simple diagnostic test on the urine has been devised. The test depends upon the presence of large amounts of 5-HIAA in the urine (Fig. 6).

Fig. 5.—Metabolic chart.

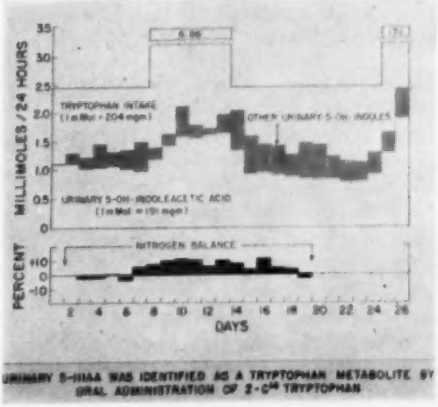


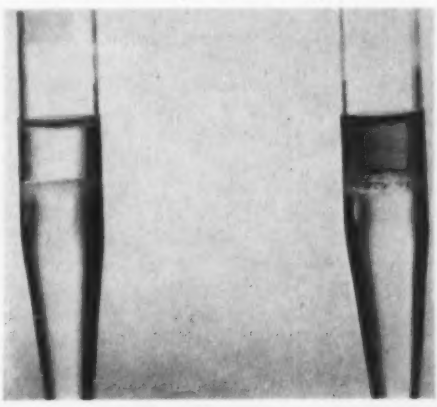
TABLE 2.—*Serotonin and Its Metabolites in Carcinoid Patients*

		Blood Serotonin, γ/Ml.	Urine 5-HIAA, Mg./24 Hr.	Total Urine 5-OH-Indoles Mg./24 Hr.
Normals		0.1-0.3	2-9	.....
Malignant carcinoid	I	2.5	320-392	453
	II	2.4	180	244
	III	0.5-1.5	240-280	345-385
	IV	2.2	28	.....
	V	1.2-1.9	380-580	460-565
	VI	.....	248	322
	VII	1.7-2.7	214-572	336-640

Reagents.—The reagents are as follows: 1-nitroso-2-naphthol—0.1% in 95% ethanol. Nitrous acid—Prepare fresh by adding 0.2 ml. 2.5% $NaNO_2$ to 5 ml. $2NH_2SO_4$. Ethylene dichloride.

Procedure.—Run a normal urine for comparison. Pipette into test tube: 0.2 ml. urine, 0.8 ml. water, 0.5 ml. 1-nitroso-2-naphthol. Mix. Then 0.5 ml. nitrous acid. Mix. Let stand at room temperature for 10

Fig. 6.—Photograph of color test. Sample on the left is normal; one on the right, carcinoid.



minutes. Then shake with 5 ml. ethylene dichloride. If turbidity results, the tube should be centrifuged.

Interpretation.—A positive test is indicated by a purple color in the top layer. No purple color will be seen with normal urine, though a slight yellow may be noticed. Assuming an average 24-hour urine volume of 1000 ml., a purple color will be seen at levels of 5-HIAA excretion as low as 30 mg. per 24 hours. At higher levels the color is more intense, and it is almost black at levels above 300 mg. per 24 hours. Therapy with chlorpromazine has been found to quench the color reaction, and a red color may be seen occasionally due to other medications. Discontinuance of all medications will alleviate such difficulties.

Clinical and Metabolic Implications

A comparison of tryptophan metabolism in normal and carcinoid patients is shown in Figure 7.

Correlation of Clinical and Metabolic Findings.—1. Overproduction of serotonin: This naturally occurring amine is known to have a potent action on smooth muscle. It may be directly responsible for the cutaneous flushes, asthma, and intestinal hypermotility.

2. Deficit of other tryptophan metabolites: (*a*) niacin deficiency—cutaneous lesions of pellagra noted in several cases; (*b*) protein deficiency—loss of weight and tissue substance.

The combined effect of these findings should be considered in any explanation of the pathophysiology, particularly with regard to the endocardial and valvular heart lesions (usually pulmonic stenosis or tricuspid insufficiency, or both) which are late manifestations of the syndrome.

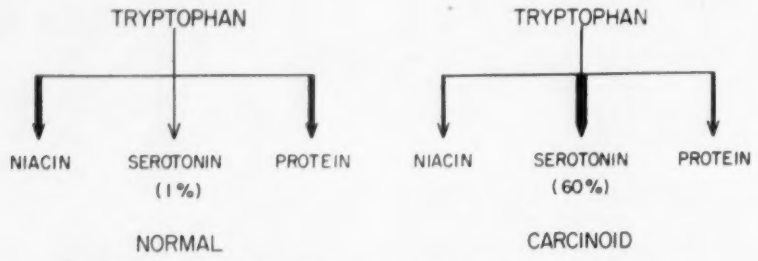


Fig. 7.—Pathways of tryptophan metabolism in normal and carcinoid.

Addendum

Analyses have been done in 20 additional carcinoid patients with the daily excretion of 5-HIAA ranging from 17-665 mg. It is likely that in three cases the primary tumor originated in lung as a bronchial adenoma of "carcinoid type."

Books

EDITED BY WILLIAM B. BEAN, M.D.

BOOK REVIEWS

Challenges to Contemporary Medicine. By Alan Gregg. Price, $3. Pp. 120. Columbia University Press, 2960 Broadway, New York 27, 1956.

If for a brief and strange interlude all people could behave rationally, and if we could take a long view of the future of our country and the future of medicine as it affects our people, our society, and our culture, many things which we do would be stopped and many things which need to be done might at least get started. Some such theme is central to Alan Gregg's searching and compassionate view of contemporary society as the patient and "Greater Medicine" as a much desired form of specific therapy. The first penetrating question he raises is how dear is life? That is, what is it worth? The implication is that human life may be looked upon as losing some of its value in a time of vast and increasing material prosperity, a difficulty illustrated in the Chinese proverb "To share poverty is easy; to share wealth, difficult." Faced with the realization that technologically we know how to treat a vast number of diseases, we do not make the best of the distribution of medical care; we have not approached realistically the problems or the needs of preventive medicine in an aging society; our older people particularly when they retire or lose the threads of their earlier existence may be a blight to themselves and a bane to their families. Even the relatively moderate achievements of psychiatry are used too little or too late. Not only do we fail to prevent illness, but we fail to provide for such illness and accidents as are inevitable by a failure of wise insurance. Dr. Gregg emphasizes the fact that into any insurance policy should be built some provision for sustaining the still magnificent but greatly overstrained structure of contemporary medical education and research in medical schools and hospitals. To this I would add that while insurance for hospitalization has been effective, insurance for major diseases, the insidious catastrophes which last a long time but do not require an operation, has never been faced realistically by the majority of insurance companies. Until man becomes universally a creature of high morals and upstanding ethics, no scheme of insurance can be satisfactory in which illness does not cost the patient a fraction of the total cost. In short, when it is cheaper for a patient to be in a hospital than to be studied and treated in an office, the patient, sometimes abetted by the doctor, will wangle his way in. Unless something like the deductible automobile insurance or the principle of coinsurance which the patient pays a percentage of the cost of illness, temptation leads to abuse by patient, by physician, and by hospital which may prove fatal to the general system. The British have learned this to their frustrated vexation.

In another very perceptive chapter, Gregg analyzes the meaning of disease and points out how to a degree each society by its beliefs, customs, and practices produces its own diseases. If in our lonely cities society puts exhorbitant demands on people not prepared emotionally, physically, or mentally for such strains, perceptive physicians have always recognized some diseases as having some causal elements in the environment as well as those in the patient. Just as no sick man can be evaluated clearly or treated warmly without keeping in mind all the many contexts of his life, so medicine cannot be divorced from the complex socioeconomic matrix in which it exists. Without expressing the thought directly, Gregg emphasizes many factors which show that medicine needs its own internal critics and critiques if it is to achieve what he looks upon as *summum bonum* or the realizing of potentials of "Great Medicine."

Those who have learned to treasure the speeches and writings of Alan Gregg will not be disappointed in this masterpiece of friendly criticism of medicine as it stands

today. Here are no quarrelsome or capricious pricks from deftly aimed needles, but words of wisdom and suggestion for action from one who is rightly looked upon as the Nestor of American medicine.

WILLIAM B. BEAN, M.D.

Dermatology. By Donald M. Pillsbury, Walter B. Shelly, and Albert M. Kligman. Price, $20. Pp. 1331, profusely illustrated. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1956.

At a casual glance one would suppose that the field of dermatology was well covered by standard textbooks to the extent that there was hardly room or need for a new one. To be sure, in a rapidly evolving field there may be necessity for such frequent orientations that a new kind of textbook is needed to illustrate or pave the way for a new approach toward medical problems in general, or in special fields. Most advancing areas in medicine soon find themselves in the realm of chemistry, with emphasis on enzymes, energy, and those central and complicated problems of the replication of nuclear material required in the manufacture of each new cell. The authors are well qualified to illustrate the new trends in dermatology. They themselves have done research which had led to significant advances and progress in a field full of inherent difficulties. These difficulties have been aided and abetted by the fragmentation of dermatology away from general medicine. The reorientation of dermatology is indicated by the sections into which this book is divided: Applied Basic Principles of Dermatology, Basic Principles and Clinical Applications of Allergy and Hypersensitivity, Principles of Diagnosis, Dermatologic Therapy, and, finally, Cutaneous Medicine. Textbooks of dermatology have now become so big that they have to read on a table or desk. This is too bad, but inevitable, since the heavy paper needed for illustrations greatly increases the weight of the book. One of the very strong features of this book is the excellent illustrations, which are extremely helpful to internists whose knowledge of dermatology may be meager but who need a reference book. In reviewing various sections of this book, I have found some unevenness. This is not altogether a reflection on the unevenness of general knowledge and understanding of various diseases, but partly the emphasis on special fields of research. The concentration on physiology and chemistry has not squeezed out the necessary information about the morphologic and diagnostic as well as the therapeutic aspects of various diseases of the skin.

In any field, the more one knows the more critical one becomes of writing and discussions in that area. I was somewhat disappointed in the treatment of vascular lesions of the skin, to which I have given much attention, but perhaps they got no less than they merited.

One still misses in writings on skin disease a detailed consideration of ecology, a scholarly comprehension of the secular trend of lesions, and, perhaps most of all, a true understanding of reasons for localization, for the size, for the extent, and for the behavior of single lesions in many disorders of the skin. In short, now that we are working on an understanding of the minute housekeeping of each individual cell in the skin and know something of its function, its energy requirements, its enzymes systems, its structures, and its diseases, we still need to continue investigations with a broader pattern of skin disease. We must learn the minute natural history of lesions and people who harbor lesions in the skin.

All in all, this book is excellent for internists and should provide not only a ready reference book for those who wish to study but a clearer and deeper understanding of those aspects of the skin which are an important central theme in so many areas of what has most unhappily come to be called internal medicine. No internist can be well versed in his field without a detailed knowledge of disorders of the skin, and no dermatologist can do a proper job without such knowledge of general medicine.

WILLIAM B. BEAN, M.D.

James Parkinson (1755-1824): A Bicentenary Volume of Papers Dealing with Parkinson's Disease, Incorporating the Original "Essay on the Shaking Palsy." Edited by Macdonald Critchley. Price, $4.50. Pp. 268, with illustrations. St. Martin's Press, Inc., 103 Park Ave., New York 17, 1955.

Of those who have achieved eponymic "immortality," very few deserve this boon of fickle fate more than James Parkinson. This book was brought out in 1955, on the

occasion of the bicentenary of Parkinson's birth. In addition to reproducing in facsimile "An Essay on the Shaking Palsy," the editor has brought together a very perceptive biographical essay on Parkinson, by McMenemey; a review of the pathology of Parkinson's disease, by Greenfield, and a clinical analysis of the paralysis agitans syndrome, by Sir Francis Walshe, whose firm critical strokes have done so much to keep English neurology centered on clinical experience, corrected and refreshed by an appeal to natural history as well as the fancier but sometimes more fanciful formulations of the electroneurophysiologists. Before reading this book my ignorance of the man James Parkinson was complete, in fact, a perfect thing. This has all been changed by reading his "Essay" and learning something of his remarkably productive life as a practicing physician, his honest and courageous liberalism at a time when the reactionary forces of the post-French-revolution era were tending to become almost as excessive as had been the horrors of the mob rule in France. To those who are interested in medical history and who gradually come to realize how important the individual doctor is in the advance of medicine and how important in any doctor's life is the time and place and epoch in which he lives, these essays will provide refreshment and delight. Especially in a new country like the United States, we would do well to emulate our British comrades in medicine in tributes to their illustrious medical forebears. For neither men nor medicine are likely to advance unless we can recognize and pay tribute to elements of greatness in those who have gone before. In fact, such a posture might in some small degree encourage not only a recognition of greatness on the contemporary medical scene but even greatness itself.

WILLIAM B. BEAN, M.D.

Psychologic Aspects in the Care of Infants and Children. Summary of Pediatric Research Conference. No charge. Pp. 90. Ross Laboratories, Columbus 16, Ohio, 1956.

This booklet is a summary of the Ross Laboratories' Twenty-First Research Conference and is available to interested physicians without charge. A number of problems related to psychosocial factors are discussed extensively: To what extent should this subject be emphasized, when and how it should be introduced in student and resident training, and how it can be best implemented. These topics are made particularly interesting and provocative by the variety of professional background of the participants in the conference. Pediatricians, psychiatrists, and social workers describe their efforts to incorporate this material into the teaching of several medical schools and in varying types of pediatric practices.

The definition of the role of the pediatrician in practice is considered and revealed to be not too well delineated. Is the pediatrician the most logical person to be the family counsellor? Is he prepared to do so by virtue of his education and training in the amount of available time? Is it and should it be possible for the pediatrician to fulfill this role in the face of the heavy demands upon his time and the general reluctance of the parents to pay commensurate fees for this type of advice? The consideration of all of these questions leads to a very timely and interesting discussion, which is equally apropos to the problems confronting the internist and the general physician. My only criticism would be that all of the participants were obviously enthusiastic and convinced of the necessity for increased emphasis on sociopsychologic factors. There are those who do not subscribe wholeheartedly to these views, and perhaps the conference would have been more profitable to have had the latter opinions expressed also.

GEORGE R. BARNES JR., M.D.

The Happy Life of a Doctor. By Roger I. Lee, M.D. Price, $4. Pp. 278. Little, Brown & Company, 34 Beacon St., Boston 6, 1956.

Doctors may write freely about how to invest profits, how they have managed to become such a great success, the general decline of medicine, or the dance of death. They write a great variety of scientific papers, books, monographs, and essays. Autobiography by doctors is rarer, perhaps, because it carries more than the average risk which resides in autobiography. If authors are successful physicians, they may actually come to believe what patients tell them, scarcely realizing that what masquerades as worldly wisdom is probably intellectual innocence. Still, a perceptive medical autobiography may give the reader an opportunity to get some insights into why people

study medicine and how they become successful enough to see that a chronicle of their lives would be of some use and interest. Few doctors are willing to search their souls, and few who have done so are willing to share the findings with the world.

This is a pleasant book to read. The story is told with a chuckle, a twinkle, and occasionally a roar of laughter. It is an excellent book, a cheerful book, and one that is very well named. Dr. Lee doesn't really tell us much about his motives for getting into medicine. At least part of his motivation may have been an effort to escape other careers in which his stuttering might have exposed him to more vexation in dealing with people. His triumphant attack on stuttering by reading, relaxing, and growing fat seems to have annoyed psychoanalysts, who can scarcely believe in such simple therapy.

Dr. Lee brought a well-trained intellect and a warm personality into a career which made him a successful practitioner, medical statesman, soldier, and teacher. His iconoclasm and his joyful heresy must have made him a delightful companion, physician, and parent. His life spans the last 50 years in medicine, a period during which developments in science and medicine have exploded in a logarithmic phase of increase. The peoples, the places, and the behind-the-scenes manipulations are disclosed in a charming way, somewhat offhand, as though one were overhearing a pleasant conversation. Among the interesting features of the book are occasional commentaries about epitaphs. On page 32, Dr. Frederick C. Shattuck is said to have remarked that he wanted put on his gravestone "He fed typhoid fever." This is an interesting echo from Graves, who once said he wished on his tombstone the simple words "He fed fevers." The end of the book is a pleasant series of possible epitaphs for Dr. Lee by Dr. Lee.

To an outsider not initiated into the revered mysteries of Harvard and the Harvard Corporation, the obsequious genuflections in this direction strike one as the only discordant note. I venture to say this would not be a discordant note to those who by fate or design are permitted to drink of its heady waters.

This book should be enjoyed by physicians and laymen alike. It would make a good present for a physician or for anyone somehow missed from last season's Christmas list. Medical students from twenty to a hundred should enjoy it.

WILLIAM B. BEAN, M.D.

Fundamentals of Immunology. Third edition. By W. C. Boyd. Price, $10. Pp. 776, with 74 illustrations. Interscience Publishers, Inc., 250 Fifth Ave., New York 1, 1956.

In his preface to the third edition of "Fundamentals of Immunology," the author states the purpose is to introduce the science of immunity primarily to students and research workers. The book accomplishes this purpose. It is concerned, however, much more with treatment of the chemical than with the biological aspects of immunity. This is unfortunate. The chemical approach appears to be the key which will undoubtedly give us the truth concerning biological mechanisms, but flexibility in thinking, in learning, and in investigation of life processes must be held in areas where chemical precision cannot yet be applied. Thus the history, variability, theory, and techniques which have formed the foundation for our present understanding of biological systems must remain important in shaping our thinking for future investigation and for progress. In the light of this the considerations of complement, the hypersensitive reactions, and phagocytosis are perhaps incomplete.

The chapters on antigens, antibodies, and the antigen-antibody reactions are well written and fairly comprehensive. The chapter on cell antigens is for the most part a catalogue of the antigens of microbial pathogens. It is unfortunate that more care was not exercised in utilizing proper scientific names and species designations for a number of the organisms considered, since in several cases this might weigh heavily on the accuracy of the meaning of statements made.

The blood groups are handled very well, as one would expect from the author. The new chapter on autoimmunization is an interesting addition.

The final third of the volume is concerned with immunological investigative, diagnostic, prophylactic, and therapeutic methodology—clinical, laboratory, and technical procedures and recommendations.

WAYBURN S. JETER

CIBA Foundation Colloquia on Ageing. Vol. II. Ageing in Transient Tissues. Edited by G. E. W. Wolstenholme and Elaine C. P. Millar. Price, $6.75. Pp. 256, with 96 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6, 1956.

Who wouldn't like to know the whys and wherefores of growing old? Of late many books have been written on various aspects of this topic, and one of the most interesting of them is the little book which is the subject of this review. The unifying idea of the book is that something important about the process of aging might be learned from an investigation of the aging of tissues that have a shorter normal life than the parent organism. It was hoped such information might provide unsuspected clues and suggestions for further work on aging. Since the colloquia were designed to consider basic mechanisms and not the possible applications to human medicine, the participants were biologists, anatomists, physiologists, zoologists, and botanists.

An inspection of the table of contents gives a good idea of the scope of the book and the kind of information it contains. Five papers deal with the results of experimental studies, chiefly in rats and guinea pigs, of the regenerative capacities of the ovary and testis and the development of the cyclic changes in the sexual organs. For the most part these papers seemed to me to be primarily concerned not with problems of aging but rather with various aspects of the cyclic changes that occur in endocrine organs.

Another five papers give an account of aging of the placenta. Of these I found particularly interesting the paper by Huggett, of St. Mary's Hospital of London, on "Chronological Changes in Placental Function," in which he reports that with age the composition of the placenta does not change regularly but instead spasmodically. This is interpreted to mean that different functions are exercised at different ages. Another stimulating paper in this group is the one by Villee, of Harvard, who describes his interesting work on the biochemical changes that occur with aging.

The two papers on the aging of human red cells are fascinating. Of exceptional interest is the one by J. E. Lovelock, of London, in which he develops the thesis that deterioration of red blood cells stored in the cold is due chiefly to diffusion of substances from the cell and not to metabolic activities which are in fact largely brought to a standstill by the low temperature. His analogy of the process of aging to information theory is most provocative. Apparently, in communications engineering messages transmitted over a great distance may "age" and become unintelligible. Their rejuvenation may be accomplished if the message is received simultaneously over several different but closely adjacent paths and then combined. According to Lovelock there is "more than a casual resemblance between this device and the natural process of conjugation."

The remaining papers deal with a variety of miscellaneous topics, among which may be mentioned "The Ageing of the Axillary Apocrine Sweat Glands in the Human Female," "The Growth Cycle of Deer Antlers," and "The Metabolism of Senescent Leaves," all of which are full of interest. As is customary in the Ciba Colloquia, a full report is included of the discussions that took place, and these are most useful and stimulating.

This book does not answer many specific questions about aging and does not even propose a definition of aging which would be acceptable to all the participants in the symposium. Instead it poses questions, and in this lies the great fascination of the book. I doubt that the book will materially help us in the solution of everyday practical problems or contribute greatly to our knowledge of the aging human patient, but for the reader with curiosity and a taste for exploring the byways of biology, this book will provide pleasant reading and new things to think about.

WILLIAM B. WARTMAN, M.D.

Women of Forty: The Menopausal Syndrome. By M. E. Landau, M.D., F.R.C.S. Price, $2.50. Pp. 49. Philosophical Library, Inc., 15 E. 40th St., New York 16, 1956.

Women who are approaching the menopause usually do not do so gladly. Their admitted age in years may become immobilized as youth recedes. Some of their anxiety, usually based on a combination of ignorance and the gossipy folklore of the woman's club or the afternoon tea, may be dispelled by putting this little book in their hands. It is full of well-known and generally accepted information set forth clearly in a style that nontechnically trained people can understand. This booklet is small enough to fit

easily into a woman's all-encompassing handbag and though expensive at five cents a page might reduce the item budgeted for tranquilizers.

WILLIAM B. BEAN, M.D.

Die Leberkrankheiten: Diagnostik und Therapie für die Praxis. By Prof. Dr. Kurt Beckmann. Price, $8.60; 36 marks. Pp. 261, with 74 illustrations, in part colored. Georg Thieme Verlag, Herdweg 63, (14a) Stuttgart N, 1957.

This book presents the opinions of an experienced German clinician and thus an illuminating insight into the German concepts in hepatic diseases. The clinical symptomatology is discussed in great detail; the hepatic tests receive considerable less emphasis than the findings in liver biopsy, the peritoneoscopic method being applied in contrast to the "blind" biopsy mainly used in this country. Descriptions of the gross appearance of the liver in life supported by peritoneoscopic drawings are excellent and present features seldom illustrated in American texts. They doubtless are the part of this book most valuable for the American reader. The viewpoints of the originator of the peritoneoscopic method, Kalk, find wide considerations. The histologic descriptions, in contrast, are technically poor. The American influence is apparent throughout the book, not only in the scarce literature given, but also in the classification applied. However, many opinions may sound somewhat strange to the American reader. For instance, considerable space is devoted to chronic hepatitis as separated from cirrhosis. Gallbladder diseases following viral and other types of hepatitis are emphasized. An endogenous toxic hepatitis from protein breakdown products or as result of Graves' disease are discussed. Infectious mononucleosis is considered a focal granulomatous lesion rather than a diffuse hepatitis. A large number of therapeutic procedures are listed, and much emphasis is laid upon the heat treatment of hepatitis by several methods, as well as upon administration of liver extract in various forms of liver diseases, especially in the early stages of cirrhosis. But a healthy conservatism counteracts, to a great degree, this enumeration of the large number of procedures. In conclusion, this handsomely printed book, written for the practicing physician and especially the general practitioner, presents, in a remarkably condensed fashion, much information.

HANS POPPER, M.D.

Symposium on Vitamin Metabolism. Proceedings of a symposium held under the auspices of the University of Texas and the National Vit. Foundation, Incorporated, New York City, March 6, 1956. By G. M. Brown, J. J. Burns, I. C. Gunsalus, L. M. Henderson, J. Hurwitz, C. A. Nichol, S. Ochoa, G. W. E. Plaut, and L. D. Wright. Price, $2.50. Pp. 118. The National Vitamin Foundation, Inc., 15 E. 58th St., New York 22, 1956.

This collection of papers, which describes modern viewpoints on the cellular metabolism of the vitamins, is Number 13 of the Nutrition Symposium Series, and, like its predecessors, it is especially useful to those doing research in this field. Nine separate papers with a complete record of discussions cover many aspects of intermediary metabolism. Opening with a foreword by E. E. Snell and some generalizations by Severo Ochoa, the volume includes details on the biogenesis of riboflavin, the metabolism of thiamine, lipoic acid, nicotinic acid (niacin), pyridoxine hydrochloride (vitamin B_6), pantothenic acid, folic acid, ascorbic acid, and biotin. To those who are engaged in the modern clinical search to designate alterations in individual enzymatic reactions as functions of a diseased state, this little volume should be especially valuable in highlighting areas in which additional investigations are required and where what we know about vitamin metabolism might possibly have useful implications in medicine.

M. K. HORWITT

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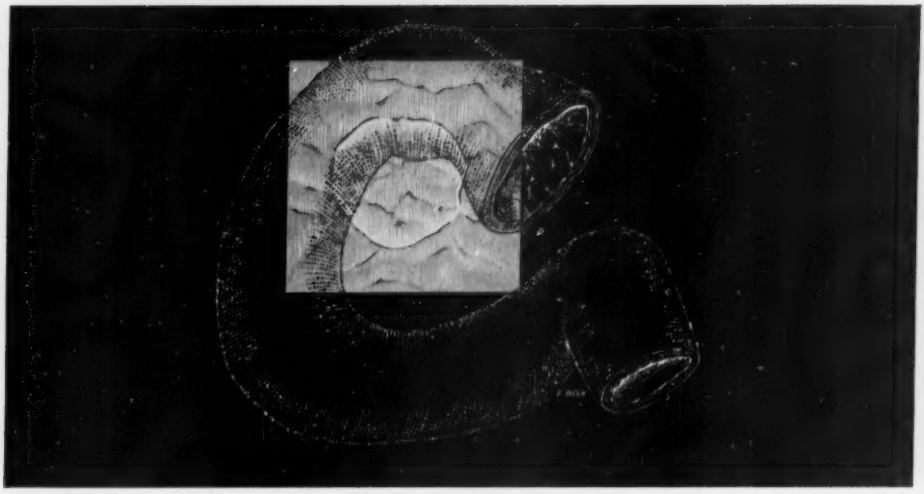

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1. Lichstein, J.; Morehouse, M. G., and Osmon, K. L.: Am. J. M. Sc. *232*:156 (Aug.) 1956.

2. Sun, D. C. H., and Shay, H.: Arch. Int. Med. *97*:442 (April) 1956.

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5. Silver, H. M.; Pucci, H., and Almy, T. P.: New England J. Med. *252*:520 (March 31) 1955.

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Marquis, D. G., Kelly, E. L., Miller, J. G., Gerard, R. W. and Rapoport, A.: Ann. New York Acad. Sc. 67:701, May 6, 1957.

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Keyes, B. L.: Pennsylvania M. J. 60:177, Feb. 1957.

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Sokoloff, O. J.: A.M.A. Arch. Dermat. & Syph. 74:393, Oct. 1956.

4 **"It ['Miltown'] . . . does not cloud the sensorium, and has a helpful somnifacient effect devoid of 'hangover'."**

Kessler, L. N. and Barnard, R. D.: M. Times 84:431, April 1956.

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Rindskopf, W., Ravreby, M., Gutenkauf, C. and Sands, S. L.: J. Iowa M. Soc. 47:57, Feb. 1957.

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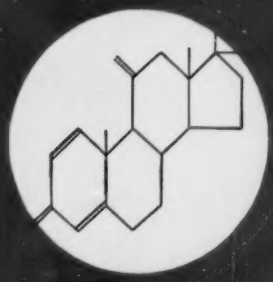

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1. Bollet, A.J., Black, R., and Bunim, J.J.: J.A.M.A. *158*:459 (June 11) 1955.

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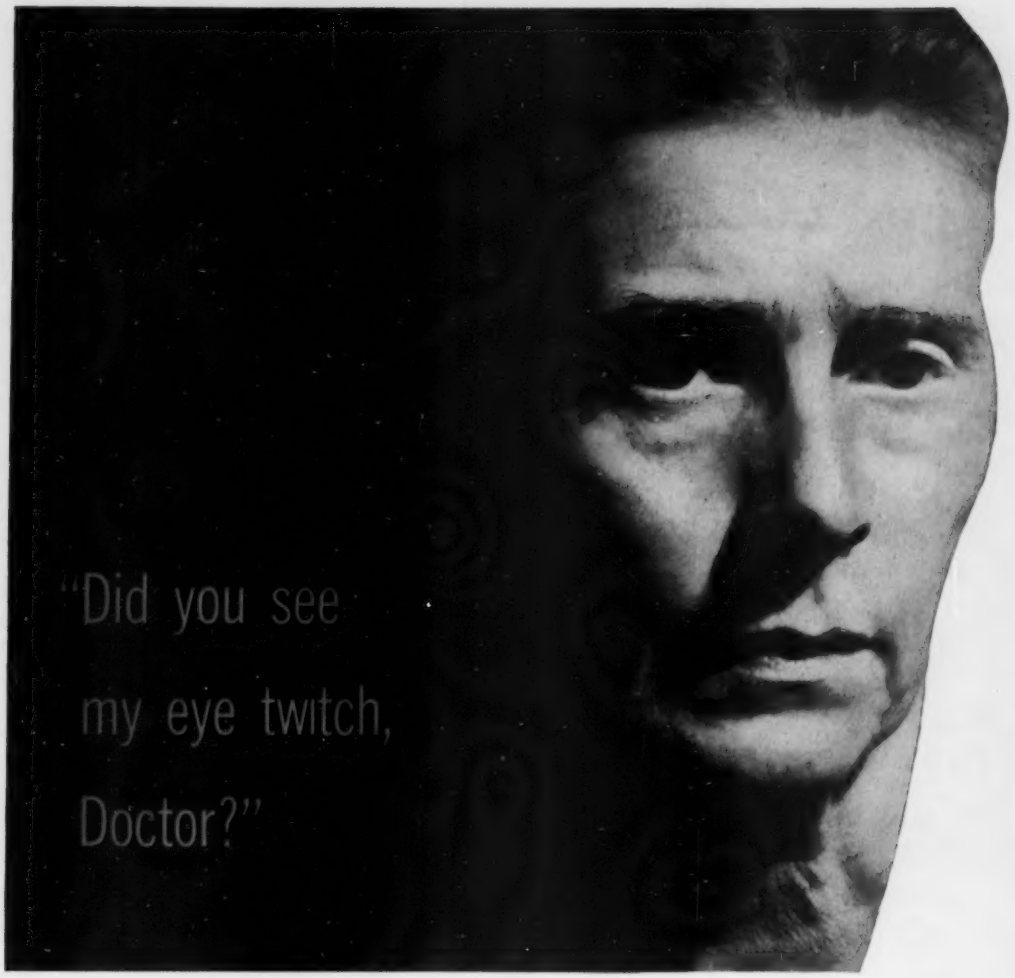

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Longmire, Wm. P., Jordan, Paul H., and Briggs, John D., Annals of Surgery, 144:4, 688, 1956

Everson, T. C., Grossman, M. I., and Ivy, A. C.: Bulletin of Amer. College of Surgeons, January, 1950.

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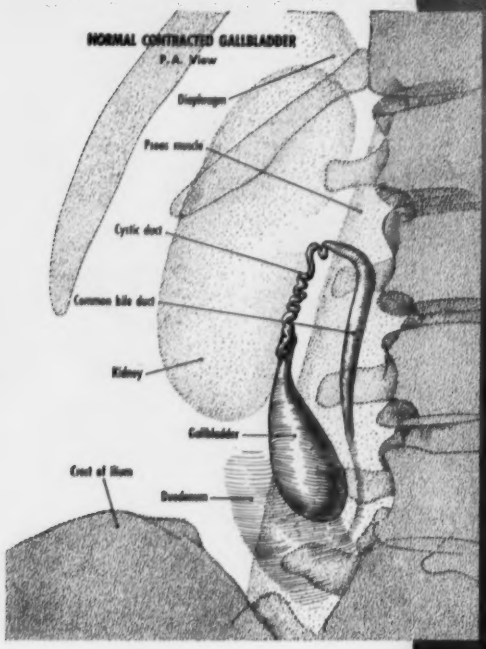

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